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Specification

20-HETE Synthase Inhibitor

Technical Field

The present invention relates to hydroxyformamidinobenzene derivatives inhibiting a synthase of 20-hydroxyeicosatetraenoic acid (20-HETE) biosynthesized from arachidonic acid.

Background Art

Sub A1

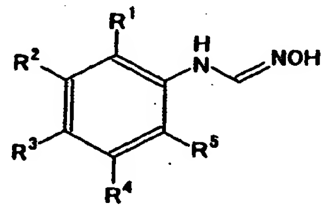
Prostaglandins produced by cyclooxygenase and lypoxygenases produced by lipoxygenase have been well known as physiologically active substances synthesized from arachidonic acid. Recently, it has been elucidated that 20-HETE, which is produced from arachidonic acid by the cytochrome P450 family enzymes, functions in various manner *in vivo* (*J. Vascular Research*, vol. 32, p.79 (1995)). It has been reported that 20-HETE induces constriction or dilation of important organs such as the kidneys and the cerebral blood vessels, and causes cell proliferation, and it is suggested that 20-HETE plays important physiological roles *in vivo*, and participates in various kidney diseases, cerebrovascular diseases, or circulatory diseases (*J. Vascular Research*, vol. 32, p. 79 (1995); *Am. J. Physiol.*, vol. 277, p. R607 (1999); and the like).

Disclosure of the Invention

An object of the present invention is to provide an inhibitor for production of 20-HETE, which participates in constriction or dilation of microvessels in the important organs such as the kidneys and the cerebral blood vessels, or in causing cell proliferation.

As a result of various studies in order to solve the above problem, the present inventors have found that aromatic compounds having a specific substructure unexpectedly possess the inhibitory activity for 20-HETE synthase, to accomplish the present invention.

That is, one mode of the present invention corresponds to an inhibitor of 20-hydroxyeicosatetraenoic acid synthase, comprising, as an effective ingredient, a hydroxyformamidine derivative represented by the general formula (1) as follows:



(1)

[wherein R^1 to R^5 are identical or different and represent a hydrogen atom; a hydroxyl group; a carboxyl group; a halogen atom; a C_{1-14} alkyl group; a C_{1-14} alkyl group substituted with 1 to 6 halogen atoms; a C_{2-5} alkenyl group; a C_{1-6} alkoxy C_{1-6} alkyl group; a C_{3-8} cycloalkyl C_{1-6} alkyl group; a C_{2-6} alkynyl group; a C_{3-8} cycloalkyl group; a C_{3-8} cycloalkoxy group; a C_{2-10} alkanoyl group; a C_{1-6} hydroxyalkyl group; a C_{1-6} hydroxyalkyl group substituted with 1 to 6 halogen atoms; a C_{2-6} alkoxycarbonyl group; a 3-phenyl-2-propenyloxycarbonyl group; a C_{2-6} alkoxycarbonyl C_{1-6} alkyl group; a di(C_{1-6} alkyl)amino C_{2-6} alkoxycarbonyl group; a mono- or di(C_{1-6} alkyl)amino group; a C_{2-10} alkanoylamino group; a C_{2-6} alkanoylamino group substituted with a C_{1-6} alkyl group; a benzoylamino group; a carbamoyl group; a carbamoyl group mono-substituted or di-substituted with C_{1-6} alkyl or phenyl groups; an N-(N',N'-di(C_{1-6} alkyl)amino C_{1-6} alkyl)carbamoyl group; a cyano group; a cyano C_{1-6} alkyl group; a nitro group; a thiol group; a phenoxy group; a phenoxy group substituted with 1 to 3 substituents from the group consisting of C_{1-6} alkyl groups, C_{1-6} alkoxy groups, and halogen atoms; a phenylthio group; a nitrophenylthio group; a C_{1-6} alkylsulfonyl group; a phenylsulfonyl group; a C_{1-6} alkylthio C_{1-6} alkyl group; a phenylsulfonyl C_{1-6} alkylthio group wherein the benzene ring is substituted with 1 to 5 halogen atoms; a phenyl group; a benzyl group; a phenyl group substituted with 1 to 3 substituents selected from the group consisting of cyano groups,

halogen atoms, C_{1-6} alkyl groups, and C_{1-6} alkoxy groups; a biphenyl group; an α-cyanobenzyl group; an α-cyanobenzyl group substituted with 1 to 5 halogen atoms; a benzyl group substituted with a bicyclo[2.2.1]-hept-5-en-2,3-dicarboxyimidyl group; a benzoyl group; a styryl group; a styryl group substituted with 1 to 5 substituents selected from the group consisting of C_{1-6} alkoxy groups and di(C_{1-6} alkyl)amino alkyl groups; a pyrrolidino group; a piperidino group; a morpholino group; a pyridyl group; a pyrimidinyl group; a pyrimidinyl group substituted with 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl groups and C_{1-6} alkoxy groups; a phthalimidoyl group; a phthalimidoyl group substituted with 1 to 3 halogen atoms; an N-carbazolyl group; a dioxopiperidinyl group substituted with 1 to 3 C_{1-6} alkyl groups; a phenylsulfonylamino group; a phenylsulfonylamino group substituted with 1 to 3 C_{1-6} alkyl groups; a C_{1-6} alkylaminosulfonyl C_{1-6} alkyl group; a thiadiazolyl group; an oxadiazolyl group; an oxadiazolyl group substituted with a substituted phenyl group wherein the substituents in the substituted phenyl group are 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and C_{1-6} alkoxy groups; a pyrrolidinyl group; a pyrazolyl group; a pyrazolyl group substituted with 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and trifluoromethyl groups; a furyl group; a furyl group substituted with 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and C_{2-6} alkoxycarbonyl groups; a thienopyrimidinylthio group; a thienopyrimidinylthio group substituted with 1 to 3 C_{1-6} alkyl groups; a thienopyridylthio group; a thienopyridylthio group substituted with 1 to 3 C_{1-6} alkyl groups; a benzothiazolylthio group; a benzothiazolylthio group substituted with 1 to 3 halogen atoms; a group represented by the formula: $-Y-(CR^{61}R^{62})_m-(CR^{63}R^{64})_n-R^7$ [wherein Y represents an oxygen or sulfur atom; R^{61}, R^{62}, R^{63}, and R^{64} are identical or different and represent a hydrogen atom, a halogen atom, a C_{1-4} alkyl group, or a trifluoromethyl group; R^7 represents a hydrogen atom; a halogen

atom; a C_{1-14} alkyl group; a C_{3-8} cycloalkyl group; a C_{3-8} cycloalkoxy group; a C_{2-10} alkenyl group; a C_{2-6} alkynyl group; a phenyl group; a phenyl group substituted with 1 to 3 substituents selected from the group consisting of nitro groups, cyano groups, C_{1-6} alkyl groups, C_{1-6} alkoxy groups, C_{1-6} alkylthio groups, phenyl groups, phenoxy groups, phenethyl groups, C_{2-6} alkoxycarbonyl groups, and halogen atoms; a cyano group; a carboxyl group; a C_{1-6} alkoxy group; a C_{1-6} hydroxyalkyl group; a C_{1-6} alkoxy C_{1-6} alkoxy group; a C_{1-6} alkoxy C_{1-6} alkoxy C_{1-6} alkoxy group; a C_{1-6} alkylthio group; a C_{2-6} alkanoyloxy group; a C_{2-6} alkanoyloxy C_{1-6} alkyl group; a phenoxy group; a phenylthio group; an N-(C_{1-6} alkyl)toluidino group; a pyrrolidino group; a piperidino group; a morpholino group; a pyridyl group; a pyridyl group substituted with a C_{1-6} alkyl group; a piperidino group substituted with a C_{1-6} alkyl group; a pyridyl group substituted with a C_{1-6} alkoxy group; a pyrrolidino group substituted with a C_{1-6} alkyl group; a morpholino group substituted with a C_{1-6} alkyl group; a morpholinyl group; a morpholinyl group substituted with a C_{1-6} alkyl group; a homomorpholinyl group; a thiomorpholino group; a thiomorpholino group substituted with a C_{1-6} alkyl group; a thiomorpholinyl group; a thiomorpholinyl group substituted with a C_{1-6} alkyl group; a piperadinyl group; a piperadin-1-yl group substituted with a C_{1-6} alkyl group at the 4-position; a homopiperidinyl group; a homopiperidinyl group substituted with a C_{1-6} alkyl group; a pyridylthio group; a quinolyl group; a furyl group; an oxetanyl group; an oxolanyl group; a dioxolanyl group; a dioxolanyl group substituted with a C_{1-6} alkyl group; an oxanyl group; a dioxanyl group; a dioxanyl group substituted with a C_{1-6} alkyl group; a benzodioxanyl group; a pyrrolidon-1-yl group; a pyrrolidinyl group; an N-(C_{1-6} alkyl)pyrrolidinyl group; a piperidinyl group; an N-(C_{1-6} alkyl)piperidinyl group; a pyrrolyl group; a thienyl group; a thiazolyl group; a thiazolyl group substituted with 1 to 3 C_{1-6} alkyl groups; a 2,6-purindion-7-yl group substituted with C_{1-6} alkyl group(s); a furfuryl group; a di(C_{1-6} alkyl)amino group; a C_{2-6} alkoxycarbonyl group; or a di(C_{1-6}

alkyl)amino C_{1-6} alkoxy group; m is an integer of 1 to 6; and n is an integer of 0 to 6]; or a group represented by the formula: $-SO_2NR^8R^9$ [wherein R^8 and R^9 are identical or different and represent a hydrogen atom, a C_{1-10} alkyl group, a C_{2-6} alkanoyl group, an isoxazolyl group, an isoxazolyl group substituted with 1 to 3 C_{1-6} alkyl groups, a thiadiazolyl group, a thiadiazolyl group substituted with 1 to 3 C_{1-6} alkyl groups, a thiazolyl group, a thiazolyl group substituted with 1 to 3 C_{1-6} alkyl groups, a pyridyl group, a pyridyl group substituted with 1 to 3 C_{1-6} alkyl groups, a pyrimidinyl group, a pyrimidinyl group substituted with 1 to 3 C_{1-6} alkyl groups, a pyrimidinyl group substituted with 1 to 3 C_{1-6} alkoxy groups, a pyridazinyl group, a pyridazinyl group substituted with 1 to 3 C_{1-6} alkoxy groups, an indazolyl group, or a carbamoyl group mono- or di-substituted with C_{1-6} alkyl groups, or alternatively, taken together with the nitrogen atom to which they are bonded, form a 3,5-dioxopiperadino group, a pyrrolidinyl group, a piperidino group, or a morpholino group], or alternatively,

the two groups adjacent to each other of R^1 to R^5, taken together with the benzene ring to which they are bonded, form a phthalimide ring; a phthalimide ring substituted with a C_{1-6} alkyl group; an indole ring; an indane ring; an indazole ring; a benzotriazole ring; an S,S-dioxobenzothiophene ring; a 2,3-dihydroimidazo[2,1-b]benzothiazole ring; a dibenzofuran ring; a dibenzofuran ring substituted with a C_{1-6} alkoxy group; a fluorene ring; a fluorene ring substituted with a halogen atom; a pyrene ring; a carbostyryl ring; a carbostyryl ring substituted with a C_{1-6} alkyl group; a naphthalene ring; a naphthalene ring substituted with 1 to 3 substituents selected from the group consisting of cyano groups, halogen atoms, nitro groups, and C_{1-6} alkyl groups; a 1,2,3,4-tetrahydronaphthalene ring; a quinoline ring; a quinoline ring substituted with a C_{1-6} alkyl group; an isoquinoline ring; a 2-oxo-α-chromene ring; a 2-oxo-α-chromene ring substituted with 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl groups, C_{1-6} alkoxy groups, and C_{1-6} alkoxy

C_{1-6} alkyl groups; a cinnolin ring; a cinnolin ring substituted with a C_{1-6} alkyl group; a phthalazindione ring; a benzothiazol ring; a benzothiazol ring substituted with a C_{1-6} alkyl group; a benzodioxorane ring; or a benzobutyrolactone ring]
or a pharmaceutically-acceptable salt thereof.

In the general formula (1) described above, it is preferable that R^1 to R^5 be identical or different and represent a hydrogen atom; a hydroxyl group; a carboxyl group; a halogen atom; a C_{1-14} alkyl group; a C_{1-14} alkyl group substituted with 1 to 6 halogen atoms; a C_{2-6} alkynyl group; a C_{3-8} cycloalkyl group; a C_{3-8} cycloalkoxy group; a C_{2-10} alkanoyl group; a C_{1-6} hydroxyalkyl group; a C_{1-6} hydroxyalkyl group substituted with 1 to 6 halogen atoms; a C_{2-6} alkoxycarbonyl group; a 3-phenyl-2-propenyloxycarbonyl group; a C_{2-6} alkoxycarbonyl C_{1-6} alkyl group; a di(C_{1-6} alkyl)amino C_{2-6} alkoxycarbonyl group; a mono- or di(C_{1-6} alkyl)amino group; a C_{2-10} alkanoylamino group; a C_{2-6} alkanoylamino group substituted with a C_{1-6} alkyl group; a benzoylamino group; a carbamoyl group; a carbamoyl group mono- or di-substituted with C_{1-6} alkyl or phenyl groups; an N-(N′,N′-di(C_{1-6} alkyl)amino C_{1-6} alkyl)carbamoyl group; a cyano group; a cyano C_{1-6} alkyl group; a nitro group; a thiol group; a phenoxy group; a phenoxy group substituted with 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl groups, C_{1-6} alkoxy groups, and halogen atoms; a phenylthio group; a nitrophenylthio group; a C_{1-6} alkylsulfonyl group; a phenylsulfonyl group; a C_{1-6} alkylthio C_{1-6} alkyl group; a phenylsulfonyl C_{1-6} alkylthio group wherein the benzene ring is substituted with 1 to 5 halogen atoms; a phenyl group; a benzyl group; a phenyl group substituted with 1 to 3 substituents selected from the group consisting of cyano groups, halogen atoms, C_{1-6} alkyl groups, and C_{1-6} alkoxy groups; a biphenyl group; an α-cyanobenzyl group; an α-cyanobenzyl group substituted with 1 to 5 halogen atoms; a benzyl group substituted with a bicyclo[2.2.1]-hept-5-en-2,3-dicarboxyimidyl group; a benzoyl group; a styryl group; a styryl group substituted with 1 to 5 substituents selected from the group consisting of C_{1-6} alkoxy

groups and di(C_{1-6} alkyl)amino alkyl groups; a pyrrolidino group; a piperidino group; a morpholino group; a pyridyl group; a pyrimidinyl group; a pyrimidinyl group substituted with 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl groups and C_{1-6} alkoxy groups; a phthalimidoyl group; a phthalimidoyl group substituted with 1 to 3 halogen atoms; an N-carbazolyl group; a dioxopiperidinyl group substituted with 1 to 3 C_{1-6} alkyl groups; a phenylsulfonylamino group; a phenylsulfonylamino group substituted with 1 to 3 C_{1-6} alkyl groups; a C_{1-6} alkylaminosulfonyl C_{1-6} alkyl group; a thiadiazolyl group; an oxadiazolyl group; an oxadiazolyl group substituted with a substituted phenyl group wherein the substituents in the substituted phenyl group are 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and C_{1-6} alkoxy groups; a pyrrolidinyl group; a pyrazolyl group; a pyrazolyl group substituted with 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and trifluoromethyl groups; a furyl group; a furyl group substituted with 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and C_{2-6} alkoxycarbonyl groups; a thienopyrimidinylthio group; a thienopyrimidinylthio group substituted with 1 to 3 C_{1-6} alkyl groups; a thienopyridylthio group; a thienopyridylthio group substituted with 1 to 3 C_{1-6} alkyl groups; a benzothiazolylthio group; a benzothiazolylthio group substituted with 1 to 3 halogen atoms; a group represented by the formula: $-Y-(CR^{61}R^{62})_m-(CR^{63}R^{64})_n-R^7$ [wherein Y represents an oxygen or sulfur atom; R^{61}, R^{62}, R^{63}, and R^{64} are identical or different and represent a hydrogen atom, a halogen atom, a C_{1-4} alkyl group, or a trifluoromethyl group; R^7 represents a hydrogen atom; a halogen atom; a C_{1-14} alkyl group; a C_{3-8} cycloalkyl group; a C_{2-10} alkenyl group; a C_{2-6} alkynyl group; a phenyl group; a phenyl group substituted with 1 to 3 substituents selected from the group consisting of nitro groups, cyano groups, C_{1-6} alkyl groups, C_{1-6} alkoxy groups, C_{1-6} alkylthio groups, phenyl groups, phenoxy groups, phenethyl groups, C_{2-6} alkoxycarbonyl groups,

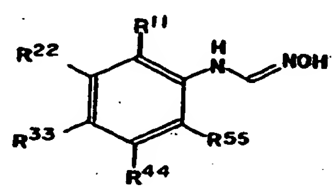
and halogen atoms; a cyano group; a carboxyl group; a C_{1-6} alkoxy group; a C_{1-6} hydroxyalkyl group; a C_{3-8} cycloalkoxy group; a C_{1-6} alkoxy C_{1-6} alkoxy group; a C_{1-6} alkoxy C_{1-6} alkoxy C_{1-6} alkoxy group; a C_{1-6} alkylthio group; a C_{2-6} alkanoyloxy group; a C_{2-6} alkanoyloxy C_{1-6} alkyl group; a phenoxy group; a phenylthio group; an N-(C_{1-6} alkyl)toluidino group; a pyrrolidino group; a piperidino group; a morpholino group; a pyridyl group; a pyridyl group substituted with a C_{1-6} alkyl group; a piperidino group substituted with a C_{1-6} alkyl group; a pyridyl group substituted with a C_{1-6} alkoxy group; a pyrrolidino group substituted with a C_{1-6} alkyl group; a morpholino group substituted with a C_{1-6} alkyl group; a morpholinyl group; a morpholinyl group substituted with a C_{1-6} alkyl group; a homomorpholinyl group; a thiomorpholino group; a thiomorpholino group substituted with a C_{1-6} alkyl group; a thiomorpholinyl group; a thiomorpholinyl group substituted with a C_{1-6} alkyl group; a piperadinyl group; a piperadin-1-yl group substituted with a C_{1-6} alkyl group at the 4-position; a homopiperidinyl group; a homopiperidinyl group substituted with a C_{1-6} alkyl group; a pyridylthio group; a quinolyl group; a furyl group; an oxetanyl group; an oxolanyl group; a dioxolanyl group; a dioxolanyl group substituted with a C_{1-6} alkyl group; an oxanyl group; a dioxanyl group; a dioxanyl group substituted with a C_{1-6} alkyl group; a benzodioxanyl group; a pyrrolidon-1-yl group; a pyrrolidinyl group; an N-(C_{1-6} alkyl)pyrrolidinyl group; a piperidinyl group; an N-(C_{1-6} alkyl)piperidinyl group; a pyrrolyl group; a thienyl group; a thiazolyl group; a thiazolyl group substituted with 1 to 3 C_{1-6} alkyl groups; a 2,6-purindion-7-yl group substituted with C_{1-6} alkyl group(s); a furfuryl group; a di(C_{1-6} alkyl)amino group; a C_{2-6} alkoxycarbonyl group; or a di(C_{1-6} alkyl)amino C_{1-6} alkoxy group; m is an integer of 1 to 6; and n is an integer of 0 to 6].

In addition, in the inhibitors of 20-hydroxyeicosatetraenoic acid synthase according to the present invention, it is preferable that in the compounds of the general formula (1), the compounds wherein R^1, R^2, R^4, and R^5 represent hydrogen atoms, or the

pharmaceutically-acceptable salts thereof, be employed as effective ingredients.

In addition, the other mode of the present invention corresponds to hydroxyformamidine derivatives having a novel chemical structure in the compounds of the general formula (1) described above or a pharmaceutically-acceptable salt thereof.

That is, the other mode of the present invention corresponds to a hydroxyformamidine derivative represented by the general formula (2) as follows:



(2)

[wherein at least one of R^{11} to R^{55} represents a C_{5-14} alkyl group; a C_{2-6} alkenyl group; a C_{3-8} cycloalkyl C_{1-6} alkyl group; a C_{2-6} alkynyl group; a C_{3-8} cycloalkyl group; a C_{3-8} cycloalkoxy group; a C_{2-10} alkanoyl group; a C_{1-6} hydroxyalkyl group; a C_{1-6} hydroxyalkyl group substituted with 1 to 6 halogen atoms; a C_{2-6} alkoxycarbonyl group; a 3-phenyl-2-propenyloxycarbonyl group; a C_{2-6} alkoxycarbonyl C_{1-6} alkyl group; a di(C_{1-6} alkyl)amino C_{2-6} alkoxycarbonyl group; a mono- or di(C_{1-6} alkyl)amino group; a C_{2-10} alkanoylamino group; a C_{2-6} alkanoylamino group substituted with a C_{1-6} alkyl group; a benzoylamino group; a carbamoyl group; a carbamoyl group mono- or di-substituted with C_{1-6} alkyl or phenyl groups; an N-(N',N'-di(C_{1-6} alkyl)amino C_{1-6} alkyl)carbamoyl group; a cyano group; a cyano C_{1-6} alkyl group; a C_{1-6} alkylsulfonyl group; a phenylsulfonyl group; a C_{1-6} alkylthio C_{1-6} alkyl group; a phenylsulfonyl C_{1-6} alkylthio group wherein the benzene ring is substituted with 1 to 5 halogen atoms; a phenyl group; a benzyl group; a phenyl group substituted with 1 to 3 substituents selected from the group consisting of cyano groups, halogen atoms, C_{1-6} alkyl groups, and C_{1-6} alkoxy groups; a biphenyl group; an α-cyanobenzyl group; an α-cyanobenzyl group substituted with 1 to 5 halogen atoms;

a benzyl group substituted with a bicyclo[2.2.1]-hept-5-en-2,3-dicarboxyimidyl group; a benzoyl group; a styryl group; a styryl group substituted with 1 to 5 substituents selected from the group consisting of C_{1-6} alkoxy groups and di(C_{1-6} alkyl)aminoalkyl groups; a pyrrolidino group; a piperidino group; a morpholino group; a pyridyl group; a pyrimidinyl group; a pyrimidinyl group substituted with 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl groups and C_{1-6} alkoxy groups; a phthalimidoyl group; a phthalimidoyl group substituted with 1 to 3 halogen atoms; an N-carbazolyl group; a dioxopiperidinyl group substituted with 1 to 3 C_{1-6} alkyl groups; a phenylsulfonylamino group; a phenylsulfonylamino group substituted with 1 to 3 C_{1-6} alkyl groups; a C_{1-6} alkylaminosulfonyl C_{1-6} alkyl group; a thiadiazolyl group; an oxadiazolyl group; an oxadiazolyl group substituted with a substituted phenyl group wherein the substituents in the substituted phenyl group are 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and C_{1-6} alkoxy groups; a pyrrolidinyl group; a pyrazolyl group; a pyrazolyl group substituted with 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and trifluoromethyl groups; a furyl group; a furyl group substituted with 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and C_{2-6} alkoxycarbonyl groups; a thienopyrimidinylthio group; a thienopyrimidinylthio group substituted with 1 to 3 C_{1-6} alkyl groups; a thienopyridylthio group; a thienopyridylthio group substituted with 1 to 3 C_{1-6} alkyl groups; a benzothiazolylthio group; a benzothiazolylthio group substituted with 1 to 3 halogen atoms; a group represented by the formula: $-Y-(CR^{61}R^{62})_m-(CR^{63}R^{64})_n-R^{77}$ [wherein Y represents an oxygen or sulfur atom; R^{61}, R^{62}, R^{63}, and R^{64} are identical or different and represent a hydrogen atom, a halogen atom, a C_{1-4} alkyl group, or a trifluoromethyl group; R^{77} represents a halogen atom; a C_{4-14} alkyl group; a C_{3-8} cycloalkyl group; a C_{2-10} alkenyl group; a C_{2-6} alkynyl group; a phenyl group; a phenyl group substituted with 1 to 3

substituents selected from the group consisting of nitro groups, cyano groups, C_{1-6} alkyl groups, C_{1-6} alkoxy groups, C_{1-6} alkylthio groups, phenyl groups, phenoxy groups, phenethyl groups, C_{2-6} alkoxycarbonyl groups, and halogen atoms; a cyano group; a carboxyl group; a C_{1-6} alkoxy group; a C_{1-6} alkoxy C_{1-6} alkoxy group; a C_{1-6} alkoxy C_{1-6} alkoxy C_{1-6} alkoxy group; a C_{1-6} hydroxyalkyl group; a C_{3-8} cycloalkoxy group; a C_{1-6} alkylthio group; a C_{2-6} alkanoyloxy group; a C_{2-6} alkanoyloxy C_{1-6} alkyl group; a phenoxy group; a phenylthio group; an N-(C_{1-6} alkyl)toluidino group; a pyrrolidino group; a piperidino group; a morpholino group; a pyridyl group; a pyridyl group substituted with a C_{1-6} alkyl group; a piperidino group substituted with a C_{1-6} alkyl group; a pyridyl group substituted with a C_{1-6} alkoxy group; a pyrrolidino group substituted with a C_{1-6} alkyl group; a morpholino group substituted with a C_{1-6} alkyl group; a morpholinyl group; a morpholinyl group substituted with a C_{1-6} alkyl group; a homomorpholinyl group; a thiomorpholino group; a thiomorpholino group substituted with a C_{1-6} alkyl group; a thiomorpholinyl group; a thiomorpholinyl group substituted with a C_{1-6} alkyl group; a piperadinyl group; a piperadin-1-yl group substituted with a C_{1-6} alkyl group at the 4-position; a homopiperidinyl group; a homopiperidinyl group substituted with a C_{1-6} alkyl group; a pyridylthio group; a quinolyl group; a furyl group; an oxetanyl group; an oxolanyl group; a dioxolanyl group; a dioxolanyl group substituted with a C_{1-6} alkyl group; an oxanyl group; a dioxanyl group; a dioxanyl group substituted with a C_{1-6} alkyl group; a benzodioxanyl group; a pyrrolidon-1-yl group; a pyrrolidinyl group; an N-(C_{1-6} alkyl)pyrrolidinyl group; a piperidinyl group; an N-(C_{1-6} alkyl)piperidinyl group; a pyrrolyl group; a thienyl group; a thiazolyl group; a thiazolyl group substituted with 1 to 3 C_{1-6} alkyl groups; a 2,6-purindion-7-yl group substituted with C_{1-6} alkyl group(s); a furfuryl group; a di(C_{1-6} alkyl)amino group; a C_{2-6} alkoxycarbonyl group; or a di(C_{1-6} alkyl)amino C_{1-6} alkoxy group; m is an integer of 1 to 6; and n is an integer of 0 to 6]; or a group represented by the formula: $-SO_2NR^8R^9$

[wherein R^8 and R^9 are identical or different and represent a hydrogen atom, a C_{1-10} alkyl group, a C_{2-6} alkanoyl group, an isoxazolyl group, an isoxazolyl group substituted with 1 to 3 C_{1-6} alkyl groups, a thiadiazolyl group, a thiadiazolyl group substituted with 1 to 3 C_{1-6} alkyl groups, a thiazolyl group, a thiazolyl group substituted with 1 to 3 C_{1-6} alkyl groups, a pyridyl group, a pyridyl group substituted with 1 to 3 C_{1-6} alkyl groups, a pyrimidinyl group, a pyrimidinyl group substituted with 1 to 3 C_{1-6} alkyl groups, a pyrimidinyl group substituted with 1 to 3 C_{1-6} alkoxy groups, a pyridazinyl group, a pyridazinyl group substituted with 1 to 3 C_{1-6} alkoxy groups, an indazolyl group, or a carbamoyl group mono- or di-substituted with C_{1-6} alkyl groups, or alternatively, taken together with the nitrogen atom to which they are bonded, form a 3,5-dioxopiperadino group, a pyrrolidinyl group, a piperidino group, or a morpholino group], or alternatively,

the two groups adjacent to each other of R^{11} to R^{55}, taken together with the benzene ring to which they are bonded, form a phthalimide ring; a phthalimide ring substituted with a C_{1-6} alkyl group; an indole ring; an indane ring; an indazole ring; a benzotriazole ring; an S,S-dioxobenzothiophene ring; a 2,3-dihydroimidazo[2,1-b]benzothiazole ring; a dibenzofuran ring; a dibenzofuran ring substituted with a C_{1-6} alkoxy group; a fluorene ring; a fluorene ring substituted with a halogen atom; a pyrene ring; a carbostyryl ring; a carbostyryl ring substituted with a C_{1-6} alkyl group; a naphthalene ring; a naphthalene ring substituted with 1 to 3 substituents selected from the group consisting of cyano groups, halogen atoms, nitro groups, and C_{1-6} alkyl groups; a 1,2,3,4-tetrahydronaphthalene ring; a quinoline ring; a quinoline ring substituted with a C_{1-6} alkyl group; an isoquinoline ring; a 2-oxo-α-chromene ring; a 2-oxo-α-chromene ring substituted with 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl groups, C_{1-6} alkoxy groups, and C_{1-6} alkoxy C_{1-6} alkyl groups; a cinnolin ring; a cinnolin ring substituted with a C_{1-6} alkyl group; a phthalazindione ring; a benzothiazol ring;

a benzothiazol ring substituted with a C_{1-6} alkyl group; a benzodioxorane ring; or a benzobutyrolactone ring, and the remaining groups of R^{11} to R^{55} are identical or different and represent a hydrogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a trifluoromethyl group, a nitro group, or a halogen atom] or a pharmaceutically-acceptable salt thereof.

In the compounds of the general formula (2), at least one of R^{11} to R^{55} may represent a C_{5-14} alkyl group; a C_{2-6} alkynyl group; a C_{3-8} cycloalkyl group; a C_{3-8} cycloalkoxy group; a C_{2-10} alkanoyl group; a C_{1-6} hydroxyalkyl group; a C_{1-6} hydroxyalkyl group substituted with 1 to 6 halogen atoms; a C_{2-6} alkoxycarbonyl group; a 3-phenyl-2-propenyloxycarbonyl group; a C_{2-6} alkoxycarbonyl C_{1-6} alkyl group; a di(C_{1-6} alkyl)amino C_{2-6} alkoxycarbonyl group; a mono- or di(C_{1-6} alkyl)amino group; a C_{2-10} alkanoylamino group; a C_{2-6} alkanoylamino group substituted with a C_{1-6} alkyl group; a benzoylamino group; a carbamoyl group; a carbamoyl group mono- or di-substituted with C_{1-6} alkyl or phenyl groups; an N-(N',N'-di(C_{1-6} alkyl)amino C_{1-6} alkyl)carbamoyl group; a cyano group; a cyano C_{1-6} alkyl group; a C_{1-6} alkylsulfonyl group; a phenylsulfonyl group; a C_{1-6} alkylthio C_{1-6} alkyl group; a phenylsulfonyl C_{1-6} alkylthio group wherein the benzene ring in the phenylsulfonyl is substituted with 1 to 5 halogen atoms; a phenyl group; a benzyl group; a phenyl group substituted with 1 to 3 substituents selected from the group consisting of cyano groups, halogen atoms, C_{1-6} alkyl groups, and C_{1-6} alkoxy groups; a biphenyl group; an α-cyanobenzyl group; an α-cyanobenzyl group substituted with 1 to 5 halogen atoms; a benzyl group substituted with a bicyclo[2.2.1]-hept-5-en-2,3-dicarboxyimidyl group; a benzoyl group; a styryl group; a styryl group substituted with 1 to 5 substituents selected from the group consisting of C_{1-6} alkoxy groups and di(C_{1-6} alkyl)amino alkyl groups; a pyrrolidino group; a piperidino group; a morpholino group; a pyridyl group; a pyrimidinyl group; a pyrimidinyl group substituted with 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl groups and C_{1-6} alkoxy

Sub A2

groups; a phthalimidoyl group; a phthalimidoyl group substituted with 1 to 3 halogen atoms; an N-carbazolyl group; a dioxopiperidinyl group substituted with 1 to 3 C_{1-6} alkyl groups; a phenylsulfonylamino group; a phenylsulfonylamino group substituted with 1 to 3 C_{1-6} alkyl groups; a C_{1-6} alkylaminosulfonyl C_{1-6} alkyl group; a thiadiazolyl group; an oxadiazolyl group; an oxadiazolyl group substituted with a substituted phenyl group wherein the substituents in the substituted phenyl group are 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and C_{1-6} alkoxy groups; a pyrrolidinyl group; a pyrazolyl group; a pyrazolyl group substituted with 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and trifluoromethyl groups; a furyl group; a furyl group substituted with 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and C_{2-6} alkoxycarbonyl groups; or a group represented by the formula: $-SO_2NR^8R^9$ [wherein R^8 and R^9 are identical or different and represent a hydrogen atom, a C_{1-10} alkyl group, a C_{2-6} alkanoyl group, an isoxazolyl group, an isoxazolyl group substituted with 1 to 3 C_{1-6} alkyl groups, a thiadiazolyl group, a thiadiazolyl group substituted with 1 to 3 C_{1-6} alkyl groups, a thiazolyl group, a thiazolyl group substituted with 1 to 3 C_{1-6} alkyl groups, a pyridyl group, a pyridyl group substituted with 1 to 3 C_{1-6} alkyl groups, a pyrimidinyl group, a pyrimidinyl group substituted with 1 to 3 C_{1-6} alkyl groups, a pyrimidinyl group substituted with 1 to 3 C_{1-6} alkoxy groups, a pyridazinyl group, a pyridazinyl group substituted with 1 to 3 C_{1-6} alkoxy groups, an indazolyl group, or a carbamoyl group mono- or di-substituted with C_{1-6} alkyl groups, or alternatively R^8 and R^9, taken together with the nitrogen atom to which they are bonded, form a 3,5-dioxopiperadino group, a pyrrolidinyl group, a piperidino group, or a morpholino group], or alternatively,

the two groups adjacent to each other of R^{11} to R^{55}, taken together with the benzene ring to which they are bonded, may form a phthalimide ring; a phthalimide ring substituted with a C_{1-6} alkyl

group; an indole ring; an indane ring; an indazole ring; a benzotriazole ring; an S,S-dioxobenzothiophene ring; a 2,3-dihydroimidazo[2,1-b]benzothiazole ring; a dibenzofuran ring; a dibenzofuran ring substituted with a C_{1-6} alkoxy group; a fluorene ring; a fluorene ring substituted with a halogen atom; a pyrene ring; a carbostyryl ring; a carbostyryl ring substituted with a C_{1-6} alkyl group; a naphthalene ring; a naphthalene ring substituted with 1 to 3 substituents selected from the group consisting of cyano groups, halogen atoms, nitro groups, and C_{1-6} alkyl groups; a 1,2,3,4-tetrahydronaphthalene ring; a quinoline ring; a quinoline ring substituted with a C_{1-6} alkyl group; an isoquinoline ring; a 2-oxo-α-chromene ring; a 2-oxo-α-chromene ring substituted with 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl groups, C_{1-6} alkoxy groups, and C_{1-6} alkoxy C_{1-6} alkyl groups; a cinnolin ring; a cinnolin ring substituted with a C_{1-6} alkyl group; a phthalazindione ring; a benzothiazol ring; a benzothiazol ring substituted with a C_{1-6} alkyl group; a benzodioxorane ring; or a benzobutyrolactone ring, and the remaining groups of R^{11} to R^{55} may be identical or different and represent a hydrogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a trifluoromethyl group, a nitro group, or a halogen atom.

In this case, it is preferable that at least one of R^{11} to R^{55} represent a C_{5-14} alkyl group; a C_{2-6} alkynyl group; a C_{3-8} cycloalkyl group; a C_{3-8} cycloalkoxy group; a C_{2-10} alkanoyl group; a C_{1-6} hydroxyalkyl group; a C_{1-6} hydroxyalkyl group substituted with 1 to 6 halogen atoms; a C_{2-6} alkoxycarbonyl group; a 3-phenyl-2-propenyloxycarbonyl group; a C_{2-6} alkoxycarbonyl C_{1-6} alkyl group; a di(C_{1-6} alkyl)amino C_{2-6} alkoxycarbonyl group; a mono- or di(C_{1-6} alkyl)amino group; a C_{2-10} alkanoylamino group; a C_{2-6} alkanoylamino group substituted with a C_{1-6} alkyl group; a carbamoyl group; a carbamoyl mono- or di-substituted with C_{1-6} alkyl or phenyl groups; an N-(N',N'-di(C_{1-6} alkyl)amino C_{1-6} alkyl)carbamoyl group; a cyano group; a cyano C_{1-6} alkyl group; a C_{1-6} alkylsulfonyl group; a phenylsulfonyl group; a C_{1-6} alkylthio C_{1-6} alkyl group; a phenyl

group; a benzyl group; a phenyl group substituted with 1 to 3 substituents selected from the group consisting of cyano groups, halogen atoms, C_{1-6} alkyl groups, and C_{1-6} alkoxy groups; a biphenyl group; an α-cyanobenzyl group; an α-cyanobenzyl group substituted with 1 to 5 halogen atoms; a benzoyl group; a pyrrolidino group; a piperidino group; a morpholino group; a pyridyl group; a pyrimidinyl group; a pyrimidinyl group substituted with 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl groups and C_{1-6} alkoxy groups; a pyrrolidinyl group; a pyrazolyl group; a pyrazolyl group substituted with 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and trifluoromethyl groups; a furyl group; a furyl group substituted with 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and C_{2-6} alkoxycarbonyl groups; or a group represented by the formula: $-SO_2NR^8R^9$ [wherein R^8 and R^9 are identical or different and represent a hydrogen atom, a C_{1-10} alkyl group, a C_{2-6} alkanoyl group, an isoxazolyl group, an isoxazolyl group substituted with 1 to 3 C_{1-6} alkyl groups, a thiadiazolyl group, a thiadiazolyl group substituted with 1 to 3 C_{1-6} alkyl groups, a thiazolyl group, a thiazolyl group substituted with 1 to 3 C_{1-6} alkyl groups, a pyridyl group, a pyridyl group substituted with 1 to 3 C_{1-6} alkyl groups, a pyrimidinyl group, a pyrimidinyl group substituted with 1 to 3 C_{1-6} alkyl groups, a pyrimidinyl group substituted with 1 to 3 C_{1-6} alkoxy groups, a pyridazinyl group, a pyridazinyl group substituted with 1 to 3 C_{1-6} alkoxy groups, an indazolyl group, or a carbamoyl group mono- or di-substituted with C_{1-6} alkyl groups, or alternatively R^8 and R^9, taken together with the nitrogen atom to which they are bonded, form a 3,5-dioxopiperadino group, a pyrrolidinyl group, a piperidino group, or a morpholino group]

and the remaining groups of R^{11} to R^{55} be identical or different and represent a hydrogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a trifluoromethyl group, a nitro group, or a halogen atom.

On the other hand, in the compounds of the general formula

(2), at least one of R^{11} to R^{55} may represent a group represented by the formula: $-Y-(CR^{61}R^{62})_m-(CR^{63}R^{64})_n-R^{77}$ [wherein Y represents an oxygen or sulfur atom; R^{61}, R^{62}, R^{63}, and R^{64} are identical or different and represent a hydrogen atom, a halogen atom, a C_{1-4} alkyl group, or a trifluoromethyl group; R^{77} represents a halogen atom; a C_{4-14} alkyl group; a C_{3-8} cycloalkyl group; a C_{2-10} alkenyl group; a C_{2-6} alkynyl group; a phenyl group; a phenyl group substituted with 1 to 3 substituents selected from the group consisting of nitro groups, cyano groups, C_{1-6} alkyl groups, C_{1-6} alkoxy groups, C_{1-6} alkylthio groups, phenyl groups, phenoxy groups, phenethyl groups, C_{2-6} alkoxycarbonyl groups, and halogen atoms; a cyano group; a carboxyl group; a C_{1-6} alkoxy group; a C_{1-6} hydroxyalkyl group; a C_{3-8} cycloalkoxy group; a C_{1-6} alkoxy C_{1-6} alkoxy group; a C_{1-6} alkoxy C_{1-6} alkoxy C_{1-6} alkoxy group; a C_{1-6} alkylthio group; a C_{2-6} alkanoyloxy group; a C_{2-6} alkanoyloxy C_{1-6} alkyl group; a phenoxy group; a phenylthio group; an N-(C_{1-6} alkyl)toluidino group; a pyrrolidino group; a piperidino group; a morpholino group; a pyridyl group; a pyridyl group substituted with a C_{1-6} alkyl group; a piperidino group substituted with a C_{1-6} alkyl group; a pyridyl group substituted with a C_{1-6} alkoxy group; a pyrrolidino group substituted with a C_{1-6} alkyl group; a morpholino group substituted with a C_{1-6} alkyl group; a morpholinyl group; a morpholinyl group substituted with a C_{1-6} alkyl group; a homomorpholinyl group; a thiomorpholino group; a thiomorpholino group substituted with a C_{1-6} alkyl group; a thiomorpholinyl group; a thiomorpholinyl group substituted with a C_{1-6} alkyl group; a piperadinyl group; a piperadin-1-yl group substituted with a C_{1-6} alkyl group at the 4-position; a homopiperidinyl group; a homopiperidinyl group substituted with a C_{1-6} alkyl group; a pyridylthio group; a quinolyl group; a furyl group; an oxetanyl group; an oxolanyl group; a dioxolanyl group; a dioxolanyl group substituted with a C_{1-6} alkyl group; an oxanyl group; a dioxanyl group; a dioxanyl group substituted with a C_{1-6} alkyl group; a benzodioxanyl group; a pyrrolidon-1-yl group; a pyrrolidinyl group; an N-(C_{1-6} alkyl)pyrrolidinyl group; a

piperidinyl group; an N-(C_{1-6} alkyl)piperidinyl group; a pyrrolyl group; a thienyl group; a thiazolyl group; a thiazolyl group substituted with 1 to 3 C_{1-6} alkyl groups; a 2,6-purindion-7-yl group substituted with C_{1-6} alkyl group(s); a furfuryl group; a di(C_{1-6} alkyl)amino group; a C_{2-6} alkoxycarbonyl group; or a di(C_{1-6} alkyl)amino C_{1-6} alkoxy group; m is an integer of 1 to 6; and n is an integer of 0 to 6], and the remaining groups of R^{11} to R^{55} may be identical or different and represent a hydrogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a trifluoromethyl group, a nitro group, or a halogen atom.

In this case, it is preferable that at least one of R^{11} to R^{55} represent a group represented by the formula: $-O-(CR^{61}R^{62})_m-(CR^{63}R^{64})_n-R^{77}$ [wherein R^{61}, R^{62}, R^{63}, and R^{64} are identical or different and represent a hydrogen atom, a halogen atom, a C_{1-4} alkyl group, or a trifluoromethyl group; R^{77} represents a di(C_{1-6} alkyl)amino group; a di(C_{1-6} alkyl)amino C_{1-6} alkoxy group; a piperidyl group; a piperidinyl group substituted with a C_{1-6} alkyl group; a piperidino group; a piperidino group substituted with a C_{1-6} alkyl group; a pyridyl group; a pyridinyl group substituted with a C_{1-6} alkyl group; a pyridinyl group substituted with a C_{1-6} alkoxy group; a pyridylthio group; a pyrrolidino group; a pyrrolidino group substituted with a C_{1-6} alkyl group; a pyrrolidon-1-yl group; a pyrrolidinyl group; a pyrrolidinyl group substituted with a C_{1-6} alkyl group; a pyrrolyl group; a thienyl group; a thiazolyl group; a morpholino group; a morpholino group substituted with a C_{1-6} alkyl group; a morpholinyl group; a morpholinyl group substituted with a C_{1-6} alkyl group; a homomorpholinyl group; a thiomorpholino group; a thiomorpholino group substituted with a C_{1-6} alkyl group; a thiomorpholinyl group; a thiomorpholinyl group substituted with a C_{1-6} alkyl group; a piperadinyl group; a piperadin-1-yl group substituted with a C_{1-6} alkyl group at the 4-position; a homopiperidinyl group; or a homopiperidinyl group substituted with a C_{1-6} alkyl group; m is an integer of 1 to 6; and n is an integer of 0 to 6], and the remaining

groups of R^{11} to R^{55} are identical or different and represent a hydrogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a trifluoromethyl group, a nitro group, or a halogen atom.

Sub A3

~~In addition, in the compounds of the general formula (2), the compounds wherein R^{11}, R^{22}, R^{44}, and R^{55} represent a hydrogen atom, that is, only R^3 at the para position of the hydroxyformamidino group on the benzene ring is a non-hydrogen atom substituent, are preferred.~~

It was discovered by the present inventors that the compounds of the general formulae (1) and (2) described above exhibit an inhibiting activity of 20-HETE synthase. Therefore, these compounds are useful as therapeutic agents for kidney diseases, cerebrovascular diseases, or circulatory diseases.

The terms used in the present invention are defined in the following. In the present invention, "C_{x-y}" means that the group following the "C_{x-y}" has the number of x - y of carbon atoms.

The term "halogen atom" refers to a fluorine, chlorine, bromine, or iodine atom.

The term "C_{1-4}, C_{1-6}, C_{1-8}, and C_{1-14} alkyl group" means straight-chain or branched alkyl groups having 1 to 4, 1 to 6, 1 to 8, and 1 to 14 carbon atoms, respectively. For example, as a C_{1-14} alkyl group, mention may be made of a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a tert-butyl group, a pentyl group, an isopentyl group, a hexyl group, an isohexyl group, a heptyl group, an octyl group, a nonyl group, or a decyl group, or the like.

The term "C_{1-14} alkyl group substituted with 1 to 6 halogen atoms" means a straight-chain or branched alkyl group having 1 to 14 carbon atoms, substituted with 1 to 6 halogen atoms. A methyl or ethyl group substituted with 1 to 4 halogen atoms is preferred. As an example thereof, mention may be made of a difluoromethyl group, a dibromomethyl group, a trifluoromethyl group, or a trifluoroethyl group, or the like. Among these groups, a

trifluoromethyl group is preferable.

Sub A4

~~The term "C_{2-6} alkenyl" means a straight-chain or branched alkynyl group having a double bond, and 2 to 6 carbon atoms. As an example thereof, mention may be made of an ethenyl group, a propenyl group, or a butenyl group, or the like.~~

The term "C_{2-6} alkynyl group" means a straight-chain or branched alkynyl group having a triple bond, and 2 to 6 carbon atoms. As an example thereof, mention may be made of an ethynyl group, a propynyl group, or a butynyl group, or the like.

The term "C_{3-8} cycloalkyl group" means a cyclic alkyl group having 3 to 8 carbon atoms, including, for example, a cyclopropyl group, a cyclopentyl group, or a cyclohexyl group, or the like.

The term "C_{3-8} cycloalkyl C_{1-6} alkyl group" means a group having a combined structure of a C_{3-8} cycloalkyl group and a C_{1-6} alkyl group, including, for example, a cyclopropylmethyl group, a cyclobutylmethyl group, a cyclopentylmethyl group, or a cyclohexylmethyl group, or the like.

The term "C_{1-6} alkoxy group" means a straight-chain or branched alkoxy group having 1 to 6 carbon atoms. As an example thereof, mention may be made of a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a 2,2-dimethylpropoxy group, a butoxy group, a *tert*-butoxy group, a 3-methylbutoxy group, a 3,3-dimethylbutoxy group, a 3-methylpentoxy group, or a 4-methylpentoxy group, or the like.

The term "C_{1-6} alkoxy C_{1-6} alkyl group" means a group having a combined structure of a C_{1-6} alkoxy group and a C_{1-6} alkyl group. As an example thereof, mention may be made of a methoxymethyl group, an ethoxymethyl group, a methoxyethyl group, an ethoxyethyl group, a propoxyethyl group, an isopropoxyethyl group, a butoxyethyl group, or a *tert*-butoxyethyl group, or the like.

The term "C_{3-8} cycloalkoxy group" means a cyclic alkoxy group having 3 to 8 carbon atoms, including, for example, a cyclopropyloxy group, a cyclopentyloxy group, or a cyclohexyloxy group, or the like.

The term "C_{2-10} alkanoyl group" means a straight-chain or branched alkanoyl group having 2 to 10 carbon atoms. As an example thereof, mention may be made of an acetyl group, a propionyl group, a butyryl group, an isobutylyl group, or a valeryl group, or the like. Among these groups, an acetyl group is preferable.

The term "C_{1-6} hydroxyalkyl" means a C_{1-6} alkyl group substituted with hydroxyl group(s). As an example thereof, mention may be made of a hydroxymethyl group, a 1-hydroxyethyl group, a 2-hydroxyethyl group, a 3-hydroxypropyl group, a 2,3-dihydroxyethyl group, or the like. Among these groups, a hydroxymethyl group, a 1-hydroxyethyl group, a 2-hydroxyethyl group, or a 3-hydroxypropyl group is in particular, preferable.

The term "C_{2-6} alkanoyloxy C_{1-6} alkyl group" means a group wherein the hydroxyl group(s) of above C_{1-6} hydroxyalkyl group is/are substituted with C_{2-6} alkanoyloxy group(s), including, for example, a 2,3-diacetoxyethyl group. The term "C_{1-6} hydroxyalkyl group substituted with 1 to 6 halogen atoms" means a C_{1-6} hydroxyalkyl group substituted with 1 to 6 halogen atoms. As an example thereof, mention may be made of a hydroxyfluoromethyl group, a 1-hydroxy-2-fluoroethyl group, a 2-hydroxy-2-fluoroethyl group, a 3-hydroxy-2-chloropropyl group, a 2,3-dihydroxy-3-bromopropyl group, a 1,1,1,3,3,3-hexafluoro-2-hydroxypropyl group, or the like. Among these groups, a 1,1,1,3,3,3-hexafluoro-2-hydroxypropyl group is preferable.

The term "C_{2-6} alkoxycarbonyl group" means a group having a combined structure of a straight-chain or branched C_{1-5} alkoxy group and a carbonyl group. As an example thereof, mention may be made of a methoxycarbonyl group, an ethoxycarbonyl group, a propoxycarbonyl group, an isopropoxycarbonyl group, or a butoxycarbonyl group, or the like, and among these groups, a methoxycarbonyl group or a propoxycarbonyl group is preferable.

Sub A5

The term "C_{2-6} alkoxycarbonyl C_{1-6} alkyl group" means a group having a combined structure of a C_{2-6} alkoxycarbonyl group and a C_{1-6} alkoxy group. Therefore, a C_{1-6} alkoxycarbonyl C_{1-6} alkyl group

may be represented by the general formula: $-(CH_2)_k-COOR^{14}$ (wherein k is an integer of 1 to 6; R^{14} is a C_{1-6} alkyl group), including, for example, $-CH_2COOCH_3$ (a methoxycarbonylmethyl group), $-CH_2COOCH_2CH_3$ (an ethoxycarbonylmethyl group), $-CH_2CH_2COOCH_3$ (a methoxycarbonylethyl group), $-CH_2CH_2COOCH_2CH_3$ (an ethoxycarbonylethyl group), or the like. Among these groups, an ethoxycarbonylmethyl group is particularly preferable.

The term "di(C_{1-6} alkyl)amino C_{2-6} alkoxycarbonyl" means a group having a combined structure of an amino group substituted with two C_{1-6} alkyl groups and a C_{2-6} alkoxycarbonyl group. As an example thereof, mention may be made of an N,N-diethylaminoethoxycarbonyl group, or an N,N-dibutylaminopropoxycarbonyl group, or the like. In particular, an N,N-diethylaminoethoxycarbonyl group is preferable.

The term "mono- or di(C_{1-6} alkyl)amino group" means an amino group substituted with one or two C_{1-6} alkyl groups. As an example thereof, mention may be made of a methylamino group, an ethylamino group, a dimethylamino group, or a diethylamino group, or the like. Among these groups, a dimethylamino group is preferable.

The term "C_{2-10} alkanoylamino group" means an amino group substituted with a C_{2-10} alkanoyl group, and as an example thereof, an acetylamino group may be given. In addition, as an example of "C_{2-10} alkanoylamino group substituted with C_{1-6} alkyl", mention may be made of an N-acetyl-N-methylamino group.

As an example of "carbamoyl group mono- or di-substituted with C_{1-6} alkyl or phenyl groups", mention may be made of an N-methylcarbamoyl group, a N-butylcarbamoyl group, or an N-phenylcarbamoyl group. As an example of "N-(N',N'-di(C_{1-6} alkyl)amino C_{1-6} alkyl)carbamoyl group", mention may be made of an N-(N',N'-diethylaminoethyl)carbamoyl group.

The term "cyano C_{1-6} alkyl group" means a group having a combined structure of a cyano group and a C_{1-6} alkyl group. As an example thereof, mention may be made of a cyanomethyl group, a cyanoethyl

group, or a cyanopropyl group. Among these groups, a cyanomethyl group is particularly preferable.

As an example of "phenoxy group substituted with 1 to 3 substituents selected from the group consisting of nitro groups, thiol groups, phenoxy groups, C_{1-6} alkyl groups, C_{1-6} alkoxy groups, and halogen atoms", mention may be made of a 2-methylphenoxy group, a 3-methylphenoxy group, a 4-methylphenoxy group, a 2-methoxyphenoxy group, a 3-methoxyphenoxy group, a 4-methoxyphenoxy group, a 2-chlorophenoxy group, a 3-chlorophenmoxy group, or a 4-chlorophenoxy group, or the like. Among these groups, a 2-methylphenoxy group, a 4-methylphenoxy group, a 2-methoxyphenoxy group, a 4-methoxyphenoxy group, or a 4-chlorophenoxy group is preferable.

The term "C_{1-6} alkylsulfonyl group" means a group having a combined structure of a C_{1-6} alkyl group and a sulfonyl group ($-SO_2-$). As an example thereof, mention may be made of a methylsulfonyl group, an ethylsulfonyl group, a propylsulfonyl group, an isopropylsulfonyl group, a butylsulfonyl group, an isobutylsulfonyl group, a *tert*-butylsulfonyl group, a pentylsulfonyl group, or an isopentylsulfonyl group, or the like. A methylsulfonyl group is preferable.

The term "C_{1-6} alkylthio C_{1-6} alkyl group" means a group having a combined structure of a C_{1-6} alkylthio group and a C_{1-6} alkyl group. As an example thereof, a methylthiomethyl group, or a 2-methylthioethyl group, or the like may be given, and a methylthiomethy group is preferable.

The term "phenylsulfonyl C_{1-6} alkylthio wherein the benzene ring is substituted with 1 to 5 halogen atoms" means a group having a combined structure of a substituted phenylsulfonyl group and a C_{1-6} alkylthio group. As an example thereof, a 4-chlorophenylsulfonylmethylthio group or the like may be given.

As an example of the "phenyl group substituted with 1 to 3 substituents selected from the group consisting of cyano groups, halogen atoms, C_{1-6} alkyl groups, and C_{1-6} alkoxy groups", mention

5-(m-methoxyphenyl)oxadiazolin-2-yl group, or a 5-(5-bromo-3-methoxyphenyl)oxadiazolin-2-yl group, or the like may be given.

As an example of "pyrazolyl group substituted with 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and trifluoromethyl groups", a 3-trifluoromethylpyrazolyl group or the like may be given.

As an example of "furyl group substituted with 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and C_{2-6} alkoxycarbonyl groups", mention may be made of a furyl group substituted with a methyl group, or an ethoxycarbonyl group, or the like, and more particularly, a 5-methyl-4-ethoxycarbonyl-2-furyl group or the like.

As the "thienopyrimidinylthio group substituted with 1 to 3 C_{1-6} alkyl groups", a substituted thienopyrimidinylthio group wherein the fused ring is substituted with one methyl or ethyl group is preferable, and more particularly, a group wherein a thiophene ring is substituted with a methyl group is more preferable.

As the "thienopyridylthio group substituted with 1 to 3 C_{1-6} alkyl groups", a substituted thienopyridylthio group wherein the fused ring is substituted with one methyl or ethyl group is preferable, and more particularly, a group wherein a thiophene ring is substituted with a methyl group is more preferable.

As the "benzothiazolylthio group substituted with 1 to 3 halogen atoms", a benzothiazolylthio group wherein the fused ring is substituted with one halogen atom is preferable, and more particularly, a group wherein the benzene ring is substituted with a chlorine atom is more preferable.

As the "isoxazolyl group substituted with 1 to 3 C_{1-6} alkyl groups", an isoxazolyl group substituted with one or two methyl or ethyl groups is preferable, and more particularly, a 5-methylisoxazolyl-3-yl group is more preferable.

As the "thiazolyl group substituted with 1 to 3 C_{1-6} alkyl groups", a thiazolyl group substituted with one or two methyl or

may be made of a 4-cyanophenyl group, a 4-chlorophenyl group, a 4-methylphenyl group, or a 4-methoxyphenyl group, or the like. Among these groups, a 4-cyanophenyl group is preferable. As the "α-cyanobenzyl group substituted with 1 to 5 halogen atoms", for example, an α-cyano-4-chlorobenzyl group or the like may be given.

As an example of the "styryl group substituted with 1 to 5 substituents selected from the group consisting of C_{1-6} alkoxy groups and di(C_{1-6} alkyl)amino alkyl groups", mention may be made of a 4-methoxystyryl group, or an 4-N,N-dimethylaminostyryl group, or the like.

As an example of the "pyrimidinyl group substituted with 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl groups and C_{1-6} alkoxy groups", mention may be made of a 6-methoxypyrimidin-4-yl group, or a 2-methylpyrimidin-4-yl group, or the like.

As an example of the "phthalimidoyl group substituted with 1 to 3 halogen atoms", a 5-chloro-N-phthalimidoyl group or the like may be given.

As an example of the "dioxopiperidinyl group substituted with 1 to 3 C_{1-6} alkyl groups", a 2,6-dioxo-3-ethylpiperidin-3-yl group or the like may be given.

As an example of the "phenylsulfonylamino group substituted with 1 to 3 C_{1-6} alkyl groups", a 4-methylphenylsulfonylamino group or the like may be given. As an example of the "C_{1-6} alkylaminosulfonyl C_{1-6} alkyl group", a methylaminosulfonylmethyl group or the like may be given.

As an example of the "oxadiazolyl group substituted with substituted phenyl group wherein the substituents in the substituted phenyl group are 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, and C_{1-6} alkoxy groups", mention may be made of a group wherein an oxadiazole ring is substituted with a phenyl group substituted with a *tert*-butyl group, or a methoxy group, or a bromine atom. More particularly, a 5-(p-*tert*-butylphenyl)oxadiazolin-2-yl group, a

ethyl groups is preferable.

As the "pyridyl group substituted with 1 to 3 C_{1-6} alkyl groups", a pyridyl group substituted with one or two methyl or ethyl groups, and in particular, a 2-methylpyridin-6-yl group is preferable.

As the "pyrimidinyl group substituted with 1 to 3 C_{1-6} alkyl groups", a pyrimidinyl group substituted with one or two methyl or ethyl groups is preferable, and more particularly, a 2,4-dimethylpyrimidin-6-yl group is more preferable.

As the "pyrimidinyl group substituted with 1 to 3 C_{1-6} alkoxy groups", a pyrimidinyl group substituted with one or two methoxy or ethoxy groups is preferable, and more particularly, a 4-methoxypyrimidin-6-yl group, or a 2,4-dimethylpyrimidin-6-yl group is more preferable.

As the "pyridazinyl group substituted with 1 to 3 C_{1-6} alkoxy groups", a pyridazinyl group substituted with one or two methoxy or ethoxy groups is preferable.

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The term "C_{2-10} alkenyl group" means a straight-chain or branched alkenyl group having a double bond, and 2 to 10 carbon atoms. As an example thereof, mention may be made of an ethenyl group, a propenyl group, or a butynyl group, or the like, and more particularly, a 1,5-dimethyl-4-hexenyl group, or the like.

The term "C_{1-6} alkylthio group" means a straight-chain or branched alkylthio group having 1 to 6 carbon atoms. As an example thereof, mention may be made of a methylthio group, an ethylthio group, a propylthio group, an isopropylthio group, a butylthio group, an isobutylthio group, a *tert*-butylthio group, a pentylthio group, or an isopentylthio group, or the like, and a methylthio group is particularly preferable.

The term "C_{2-6} alkanoyloxy group" means a group having a combined structure of a C_{2-6} alkanoyl group and an oxy group (-O-). As an example thereof, mention may be made of an acetyloxy group, a propionyloxy group, a butyryloxy group, an isobutyryloxy group, or a valeryloxy group, or the like.

As an example of "phenyl group substituted with 1 to 3

substituents selected from the group consisting of nitro groups, cyano groups, C_{1-6} alkyl groups, C_{1-6} alkoxy groups, C_{1-6} alkylthio groups, phenyl groups, phenoxy groups, phenethyl groups, C_{2-6} alkoxycarbonyl groups, and halogen atoms", mention may be made of a 4-chlorophenyl group, a 4-fluorophenyl group, a 2,5-difluorophenyl group, a 2,5-dichlorophenyl group, an o-phenethylphenyl group, a 4-methylthiophenyl group, a m-phenoxyphenyl group, a 4-methylphenyl group, a 3-methylphenyl group, a 2-methylphenyl group, a 2-methoxyphenyl group, a 3-methoxyphenyl group, a 4-methoxyphenyl group, a 2,3-dimethoxyphenyl group, a 2,4-dimethoxyphenyl group, a 4-methoxycarbonylphenyl group, a p-phenylphenyl group, or a m-cyanophenyl group, or the like.

The term "C_{1-6} alkoxy C_{1-6} alkoxy group" means a group having a combined structure of a C_{1-6} alkoxy group and a C_{1-6} alkoxy group. As an example thereof, mention may be made of a methoxymethoxy group, a methoxyethoxy group, an ethoxyethoxy group, or a methoxypropoxy group, or the like.

Examples of the "C_{1-6} alkoxy C_{1-6} alkoxy C_{1-6} alkoxy group" include $CH_3OCH_2CH_2OCH_2CH_2O$- and the like.

Examples of the "di(C_{1-6} alkyl)amino group" include $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)_2$, and the like.

Examples of the "di(C_{1-6} alkyl)amino C_{1-6} alkoxy group" include $-OCH_2N(CH_3)_2$, $-OCH_2CH_2N(CH_3)_2$, $-OCH_2CH_2N(CH_2CH_3)_2$, and the like.

The term "N-(C_{1-6} alkyl)toluidino group" means a group having a structure wherein a toluidino group ($CH_3-C_6H_4-NH-$) is substituted with a C_{1-6} alkyl group and preferably is substituted with a methyl or ethyl group. In particular, an N-ethyl-m-toluidino group is preferable.

The "furyl group" includes a 2-furyl or 3-furyl group.

The "oxetanyl group" has a structure of a saturated 4-membered ring having one oxygen atom as a hetero atom, and includes a 2-oxetanyl group, or a 3-oxetanyl group.

The "oxolanyl group" has a structure of a saturated 5-membered

ring having one oxygen atom as a hetero atom, and includes a 2-oxolanyl group, or a 3-oxolanyl group.

The "dioxolanyl group" refers to a mono-valent group derived by eliminating hydrogen atom from a saturated 5-membered ring having two oxygen atoms as hetero atoms (dioxolane), preferably from a 1,3-dioxolane ring. In the dioxolanyl group, the ring thereof may be substituted with C_{1-6} alkyl group(s). As an example thereof, a 2,2-dimethyl-1,3-dioxolan-4-yl group or the like may be given.

The "oxanyl group" has a structure of a saturated 6-membered ring having one oxygen atom as a hetero atom, and includes a 2-oxanyl, a 3-oxanyl group, or a 4-oxanyl group.

The "dioxanyl group" refers to a mono-valent group derived by eliminating hydrogen atom from a saturated 6-membered ring having two oxygen atoms as hetero atoms (dioxane), preferably from a 1,3-dioxane ring. In the dioxanyl group, the ring thereof may be substituted with C_{1-6} alkyl group(s). As an example thereof, a 5,5-dimethyl-1,3-dioxan-2-yl group or the like may be given.

The "benzodioxanyl group" refers to a mono-valent group derived by eliminating hydrogen atom from a benzodioxane ring, preferably a 1,4-benzodioxane ring. As an example thereof, a 1,4-benzodioxan-2-yl group or the like may be given.

The "piperidinyl group" includes a 2-piperidinyl, a 3-piperidinyl group, or a 4-piperidinyl group. In addition, in the piperidinyl group, the nitrogen atom present therein may be substituted with a C_{1-6} alkyl group, and an N-methyl-piperidinyl group is preferred.

The "piperidino group" refers to a mono-valent group derived by eliminating a hydrogen atom present on the nitrogen atom of piperidine.

The "pyridyl group" includes a 2-pyridyl group, a 3-pyridyl group, or a 4-pyridyl group. In the pyridyl group, the ring thereof may be substituted with a C_{1-6} alkyl group, preferably a methyl group. As an example thereof, a 6-methyl-2-pyridyl group may be given.

The "pyridylthio group" has a combined structure of a pyridyl

group and one thio group, and includes a pyridin-2-ylthio group, a pyridin-3-ylthio group, or a pyridin-4-ylthio group, and a pyridin-2-yl group is preferable.

The "pyrrolidino group" refers to a mono-valent group derived by eliminating a hydrogen atom present on the nitrogen atom of pyrrolidine.

The "pyrrolidon-1-yl group" includes a 2-pyrrolidon-1-yl or 3-pyrrolidon-1-yl group.

The "pyrrolidinyl group" includes a 2-pyrrolidinyl group or 3-pyrrolidinyl group. In the pyrrolidinyl group, the nitrogen atom present thereon may be substituted with a C_{1-6} alkyl group. As an example thereof, an N-methyl-2-pyrrolidinyl group or the like may be given.

The "quinolyl" includes a 2-quinolyl group, a 3-quinolyl group, a 4-quinolyl group, a 5-quinolyl group, a 6-quinolyl group, a 7-quinolyl group, or a 8-quinolyl group, and a 2-quinolyl group is preferable.

The "pyrrolyl group" includes a 1-pyrrolyl group, a 2-pyrrolyl group, or a 3-pyrrolyl group, and a 1-pyrrolyl group (N-pyrrolyl group) is preferable.

The "thienyl group" includes a 2-thienyl group, or a 3-thienyl group.

The "thiazolyl group" includes a 2-thiazolyl group, a 4-thiazolyl group, or a 5-thiazolyl group. In addition, in the thiazolyl group, the ring thereof may be substituted with a C_{1-6} alkyl group. As an example thereof, a 4-methyl-5-thiazolyl group or the like may be given.

The "morpholino group" refers to a mono-valent group derived by eliminating a hydrogen atom present on the nitrogen atom of morpholine.

The "furfuryl group" means a 2-furfuryl group.

The "2,6-purindion-7-yl group" refers to a mono-valent group derived from 2,6-purindione wherein oxo groups (=O) are bonded to the carbon atoms at the 2-position and the 6-position of the

purine ring and a group derived by eliminating the hydrogen atom present on the nitrogen atom at the 7-position. For the "2,6-purindion-7-yl substituted with C_{1-6} alkyl group(s)", it is preferable that one or two nitrogen atoms on the group be substituted with a C_{1-6} alkyl group, and in particular, a methyl group. As an example thereof, a 1,3-dimethyl-2,6-purindion-7-yl group or the like may be given.

Any two groups of R^1 to R^5 adjacent to each other in the general formula (1), taken together with the benzene ring to which they are bonded, may form the ring structures described above. In these rings, the following rings may be specially mentioned.

As the "phthalimide ring substituted with a C_{1-6} alkyl group", a ring substituted with a methyl or ethyl group is preferable, and more particularly, for example, a ring substituted with a methyl group such as an N-methyl-phthalimide ring is more preferable.

As the "dibenzofuran ring substituted with a C_{1-6} alkoxy group", a ring substituted with a methoxy or ethoxy group is preferable, and particularly, a ring substituted with a methoxy group is more preferable.

As the "fluorene ring substituted with a halogen atom", a ring substituted with a chlorine or bromine atom is preferred, and furthermore, a ring substituted with a bromine atom is more preferable.

As the "carbostyryl ring substituted with a C_{1-6} alkyl group", a ring substituted with a methyl or ethyl group is preferable and furthermore, a ring substituted with a methyl group is more preferable.

As the "naphthalene ring substituted with 1 to 3 substituents selected from the group consisting of cyano groups, halogen atoms, nitro groups, and C_{1-6} alkyl groups", a ring substituted with 1 to 3 cyano groups, halogen atoms, nitro groups, methyl groups or ethyl groups is preferable, and particularly, a ring substituted with a cyano group, a bromine or chlorine atom, a nitro group or a methyl group is more preferable.

As the "quinoline ring substituted with a C_{1-6} alkyl group", a ring substituted with a methyl or ethyl group is preferred, and in particular, a quinoline ring substituted with a methyl group is more preferable.

As the "2-oxo—α-chromene ring substituted with 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl groups, C_{1-6} alkoxy groups, and C_{1-6} alkoxy C_{1-6} alkyl groups", a ring substituted with a methyl group, an ethyl group, a methoxy group, an ethoxy group, a methoxymethyl group, a methoxyethyl group, an ethoxymethyl group, or an ethoxyethyl group is preferred, and in particular, a ring substituted with a methyl or methoxymethyl group is more preferable.

As the "cinnolin ring substituted with a C_{1-6} alkyl group", a ring substituted with a methyl or ethyl group is preferred, and in particular, a ring substituted with a methyl group is more preferable.

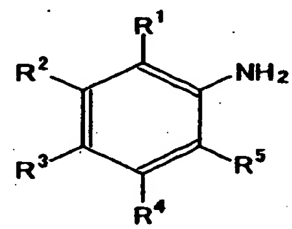
As the "benzothiazol ring substituted with a C_{1-6} alkyl group", the ring substituted with a methyl or ethyl group is preferred and furthermore, a ring substituted with a methyl group is more preferable.

In addition, in the present invention, the term "pharmaceutically-acceptable salt" refers to a salt with an alkali metal, an alkali earth metal, ammonium, an alkylammonium, or the like, as well as, a salt with a mineral acid or an organic acid. As an example thereof, mention may be made of sodium salts, potassium salts, calcium salts, ammonium salts, aluminum salts, triethylammonium salts, acetates, propionates, butyrates, formates, trifluoroacetates, maleates, tartarates, citrates, stearates, succinates, ethylsuccinates, lactobionates, gluconates, glucoheptonates, benzoates, methanesulfonates, ethanesulfonates, 2-hydroxyethanesulfonates, benzenesulfonates, para-toluenesulfonates, laurylsulfates, malates, aspartates, glutamates, adipates, salts with cysteine, salts with N-acetylcysteines, hydrochlorides, hydrobromides, phosphates,

sulfates, hydroiodides, nicotinates, oxalates, picrates, thiocyanates, undecanates, salts with polymeric acrylic acid, salts with carboxyvinyl polymers, or the like.

The compounds represented by the general formula (1) of the present invention may be prepared by or according to the methods described in Japanese Patent Application, Toku-Kai-Sho 61-165360 (which is incorporated herein by reference.)

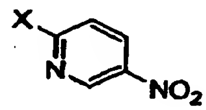
For example, the compounds of the present invention may be synthesized by reacting aniline derivatives substituted with R^1 to R^5 described below



with orthoformates such as trimethyl orthoformate, triethyl orthoformate, or the like in the presence or absence of a catalytic amount of an organic acid such as acetic acid, a mineral acid such as hydrochloric acid, or a salt of a mineral acid and an amine such as pyridine hydrochloride, for 2 to 72 hours at a temperature preferably in the range of room temperature to 150°C, and more preferably in the range of 70 to 100°C to obtain an intermediate, and subsequently treating the intermediate, after isolation or in the state as produced, with hydroxylamine in a solvent such as ethanol.

The aniline derivatives described above may be prepared, for example, by the following method. Herein, in order to simplify the explanation, the aniline derivatives wherein R^1, R^2, R^4, and R^5 are hydrogen atoms and R^3 is a group represented by the formula: $-Y-(CR^{61}R^{62})_m-(CR^{63}R^{64})_n-R^7$, are employed.

At first, a compound represented by the formula (a):



(a)

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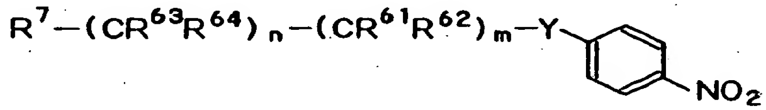
(wherein X represents a halogen atom) and a compound, for example, represented by the following formula (b):

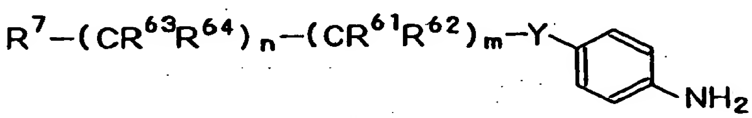
$$R^7(CR^{63}R^{64})_m-(CR^{61}R^{62})_m\ YH \qquad \text{(b)}$$

(wherein R^7, Y, R^{61}, R^{62}, m, R^{63}, R^{64}, and n have the same meanings as described above) are reacted in the presence of a base to obtain a compound represented by the following formula (c).



(c)

Subsequently, the compound represented by the formula (c) described above is derived to an aniline derivative represented by the following formula (d) by means of a general method for reducing an aromatic nitro group to an aromatic amino group.



(d)

The inhibitors for production of 20-HETE according to the present invention comprise compounds represented by the general formula (1) or the pharmaceutically-acceptable salts thereof as active ingredients, and effectively inhibit the production of 20-HETE.

In addition, the inhibitors for production of 20-HETE of the present invention are useful as medicines, and in particular, therapeutic agents for kidney diseases, cerebrovascular diseases, or circulatory diseases.

The dose of the medicines (including therapeutic agents for kidney diseases, cerebrovascular diseases, or circulatory diseases), as well as the inhibitors for production of 20-HETE according to the present invention, is preferably in a range of

1 to 2000 mg per day as the compounds represented by the general formula (1) or the pharmaceutically-acceptable salts thereof, in the case of an adult human subject to be treated. They may be administered in a single dose or divided into several doses per day. The doses may vary depending on the usage, as well as, the age, weight, and conditions of each individual patient, and the like.

The medicines (therapeutic agents for kidney diseases, cerebrovascular diseases, or circulatory diseases) as well as, the inhibitors for production of 20-HETE according to the present invention may be administered orally or parenterally, in the form of tablets, capsules, granules, powders, troches, ointments, creams, emulsions, suspensions, suppositories, injectable solutions, or the like, each of which may be produced according to the conventional formulation methods (for example, methods defined in the 12th revision of Japanese Pharmacopeia). These preparation forms may be selected depending on the conditions and ages of the patients, as well as the purpose of the treatment. Upon manufacturing preparations in various formulations, conventional fillers (for example, crystalline cellulose, starch, lactose, mannitol, or the like), binders (for example, hydroxypropylcellulose, polyvinylpyrrolidone, or the like), lubricants (for example, magnesium stearate, talc, or the like), disintegrants (for example, carboxymethylcellulose calcium, or the like), and the like, may be employed.

Best Modes for Carrying out the Invention

In the following, the present invention is illustrated in detail by the following examples. However, it should be understood that the present invention is not limited to the examples described below.

Example 1

Synthesis of

N-(4-butyl-2-methylphenyl)-N'-hydroxy-formamidine

4-Butyl-2-methylaniline (129.18 g) and ethyl orthoformate (234.66 g) were stirred for 11 hours at 100°C. Subsequently, the excess of the ethyl orthoformate was removed. The obtained crude product was dissolved in methanol (200 ml). To a methanol solution (500 ml) of hydroxylamine hydrochloride (65.59 g), a methanol solution (350 ml) of sodium methoxide (51.02 g) was added dropwise at 0°C to neutralize. The precipitated sodium chloride was filtered off. The filtrate was added dropwise to the methanol solution of the crude product, and subsequently, the mixture was stirred for 15 hours at room temperature. The methanol was removed. The obtained residue was dissolved in 800 ml of chloroform, and subsequently, washed with water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and then the solvent was removed. The obtained residue was washed with hexane to yield 63.66 g of crude crystals of the target compound. One portion of the crude crystals (35.47 g) was recrystallized from hexane : ethyl acetate (1:4) to yield 29.85 g of the target compound as a colorless powder (Compound 1 in Table 1 described below).

Melting point: 131.5 - 134.0°C

Example 2

Synthesis of

N-(4-*tert*-butylphenyl)-N'-hydroxy-formamidine

4-*tert*-Butylaniline (3.9 g) and ethyl orthoformate (7.9 g) were stirred for 6.5 hours at 100°C. Subsequently, the excess of the ethyl orthoformate was removed. The obtained crude product was dissolved in methanol (10 ml). To a methanol solution (20 ml) of hydroxylamine hydrochloride (2.1 g), a methanol solution (15 ml) of sodium methoxide (1.6 g) was added dropwise at 0°C to neutralize. The precipitated sodium chloride was filtered off. The filtrate was added dropwise to the methanol solution of the crude product, and subsequently, the mixture was stirred for 1.5

hours at room temperature. The methanol was removed. The obtained residue was dissolved in 50 ml of chloroform, and subsequently, washed with water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and then concentrated. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4:1) to yield 1.65 g of the target compound (Compound 2 in Table 1 described below).

Melting point: 113.5 - 114.5°C

Example 3

Synthesis of

N-(4-methoxycarbonylphenyl)-N'-hydroxyformamidine

A mixture of 4-aminobenzoic acid methyl ester (1.98 g) and ethyl orthoformate (4.07 g) was stirred for 16 hours at 100°C. Subsequently, the excess of the ethyl orthoformate was removed. To the obtained residue, a methanol solution (16 ml) of hydroxylamine prepared from hydroxylamine hydrochloride (1.50 g) and sodium methoxide (1.10 g) was added, and the mixture was stirred for 6 hours at room temperature. The solvent was removed and subsequently, to the residue, chloroform was added. Subsequently, it was washed successively with water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed. The residue was purified by silica gel column chromatography (eluent; n-hexane : ethyl acetate), and subsequently, by recrystallized from chloroform - methanol to yield the target compound (Compound 123 in Table 1 described below) (0.32 g) as a colorless powder.

Melting point: 167.0 - 167.5°C

Example 4

Synthesis of

N-(2-aminosulfonylphenyl)-N'-hydroxyformamidine

A mixture of 2-aminobenzsulfonamide (3.0 g), ethyl orthoformate (5.15 g), and ethyl acetate (20 ml) was stirred for

5 hours at 100°C. Subsequently, the excess of the ethyl orthoformate was removed. To a methanol solution (30 ml) of the residue, a methanol solution (40 ml) of hydroxylamine prepared from hydroxylamine hydrochloride (1.50 g) and sodium methoxide (1.10 g) was added, and the mixture was stirred for 2 days at room temperature. The solvent was removed and subsequently, to the residue, chloroform was added, and washed successively with water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed. The residue was purified by silica gel column chromatography (eluent: ethyl acetate) to yield the target compound (Compound 236 in Table 1 described below) (0.73 g) as a colorless powder.

Melting point: 130.5 - 131.5°C

Example 5

Synthesis of N-[4-(pyridin-2-ylmethoxy)phenyl]-N'-hydroxyformamidine

A mixture of 4-(pyridin-2-ylmethoxy)aniline (1.715 g) and ethyl orthoformate (2.613 g) was stirred for 14 hours at 100°C. Subsequently, the excess of the ethyl orthoformate was removed. To a methanol solution (20 ml) of the residue, a 1M methanol solution (10 ml) of hydroxylamine was added, and the mixture was stirred for 2.5 days at room temperature. The solvent was removed and subsequently, to the residue, chloroform was added. Subsequently, it was washed with water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed. The obtained residue was purified by recrystallization from ethyl acetate to yield the target compound (Compound 345 in Table 1 described below) (0.524 g) as a colorless powder.

Melting point: 159.5 - 161.0°C

Example 6

Synthesis of N-[4-(benzylthio)phenyl]-N'-hydroxyformamidine

A mixture of 4-(benzylthio) aniline (1.18 g) and ethyl orthoformate (1.78 g) was stirred for 12 hours at 100°C. Subsequently, the excess of the ethyl orthoformate was removed. To a methanol solution (20 ml) of the residue, a 1M methanol solution (10 ml) of hydroxylamine was added, and the mixture was stirred for 2.5 days at room temperature. The solvent was removed and subsequently, to the residue, chloroform was added. Subsequently, it was washed with water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed. The obtained residue was recrystallized from ethyl acetate to yield the target compound (Compound 441 in Table 1 described below) (0.43 g) as a colorless powder.

Melting point: 166°C

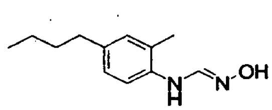
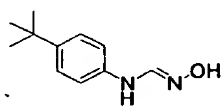
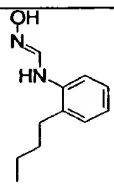
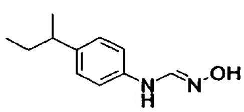
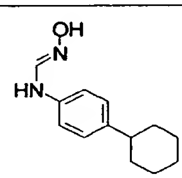
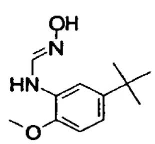
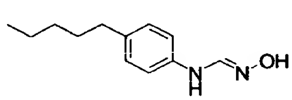
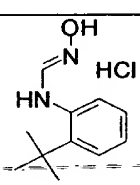
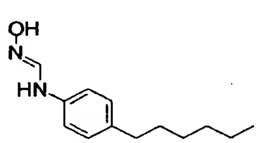
Example 7

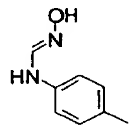
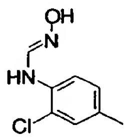
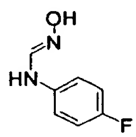
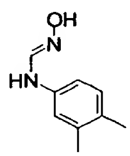
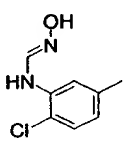
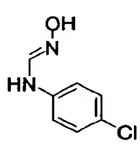
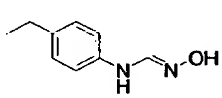
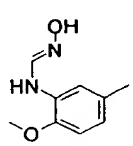
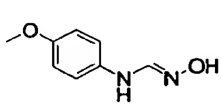
Sub A8

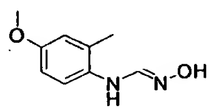
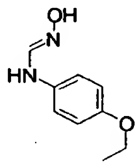
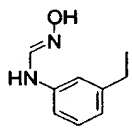
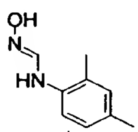
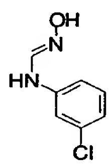
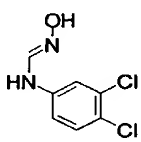
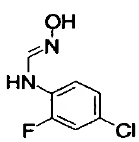
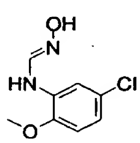
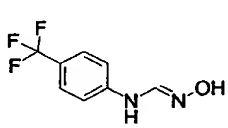
~~The compounds shown in Table 1 described below were obtained by carrying out the similar procedures as those of Production Example 1. The compounds obtained in Production Examples 1 to 6, together with the other compounds are also shown in Table 1.~~

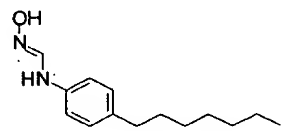
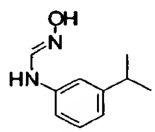
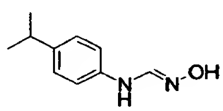
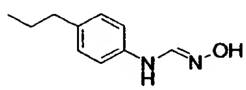
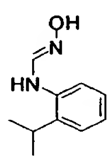
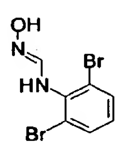
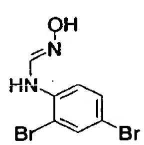
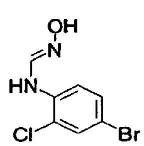
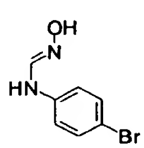
The Rf values in Table 1 corresponds to the Rf values in the case of development with a mixture of ethyl acetate : hexane (1:2) (no mark) or in the case of development with a mixture of chloroform : methanol (9:1) (marked as *), employing thin layer chromatography Silica gel 60 F_{254}, produced by Merck, or NH-TLC plates, produced by Fuji Silysia Chemical Ltd. In addition, the term "posi" or "nega" denotes data of the cation peak (M+H) or the anion peak (M-H), observed in a positive mode or a negative mode upon measurement of mass spectrum by means of the ESI method.

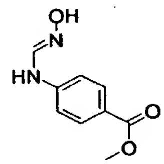
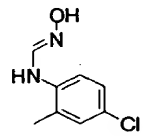
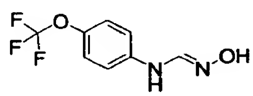
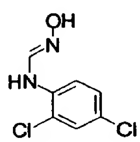
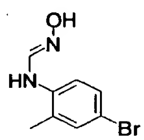
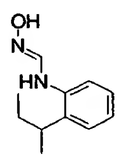
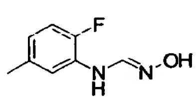
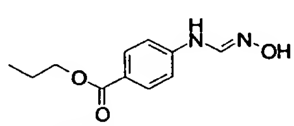
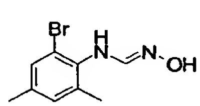
Table 1

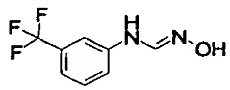
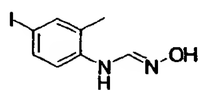
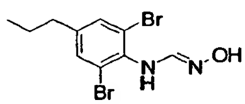
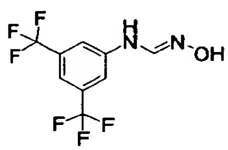
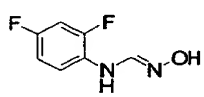
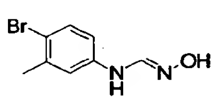
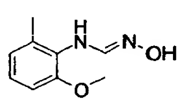
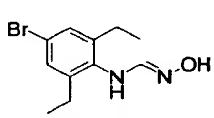
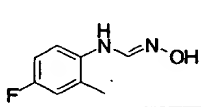
Comp.	Chemical Structure	mp.	M+H (ESI)	M+H (APCI)	M−H (ESI)	M−H (APCI)	Rf value	TLC *	Developing solvent	Inhibition rate (1 μM)	IC50 (nM)
Comp. 1		131.5 – 134.0	207	207		205	0.56	Si02 (NH)	EtOAc: MeOH =95:5	100.5	3.5
Comp. 2		113.5 – 114.5	193		191		0.13	Si02	Hexane :AcOEt =2:1	97.0	7.8
Comp. 3		84.5– 85.5	193		191		0.22	Si02	Hexane :AcOEt =2:1	98.9	
Comp. 4		101.0 – 102.5			191		0.15	Si02	Hexane :AcOEt =2:1	107.6	3
Comp. 5		153.0 – 154.0	219		217		0.13	Si02	Hexane :AcOEt =2:1	99.9	3.8
Comp. 6		119.5 – 120.5	223		221		0.20	Si02	Hexane :AcOEt =2:1	99.9	
Comp. 7		122.5 – 124.0	207		205		0.14	Si02	Hexane :AcOEt =2:1	110.5	12.1
Comp. 8		141.0 – 142.0	193		191		0.21	Si02	Hexane :AcOEt =2:1	99.9	
Comp. 9		108.0 – 110.0	221		219		0.15	Si02	Hexane :AcOEt =2:1	99.9	4.9

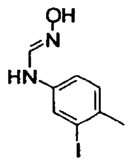
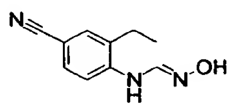
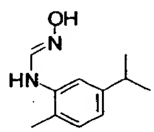
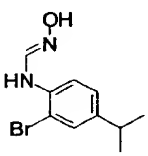
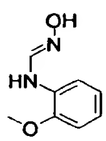
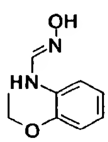
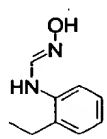
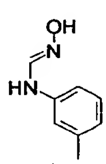
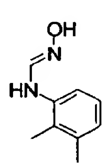
Comp. 10		143.5 – 144.5			151		0.12	Si02	Hexane :AcOEt =2:1	89.5	669.0
Comp. 11		151.0 – 152.5	185		183		0.18	Si02	Hexane :AcOEt =2:1	92.7	297.1
Comp. 12		139.5 – 140.5	155				0.08	Si02	Hexane :AcOEt =2:1	77.1	1415.5
Comp. 13		116.0 – 118.0	165		163		0.12	Si02	Hexane :AcOEt =2:1	95.9	117.9
Comp. 14		151.0 – 153.0			183		0.19	Si02	Hexane :AcOEt =2:1	91.7	162.8
Comp. 15		155.5 – 156.0	171		169		0.10	Si02	Hexane :AcOEt =2:1	92.9	287.7
Comp. 16		141.0 – 142.0	165		163		0.12	Si02	Hexane :AcOEt =2:1	97.6	6.6
Comp. 17		136.5 – 139.0	181		179		0.15	Si02	Hexane :AcOEt =2:1	85.3	
Comp. 18		139.0 – 140.0	167		165		0.06	Si02	Hexane :AcOEt =2:1	94.6	45.2

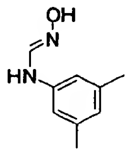
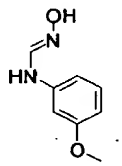
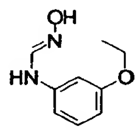
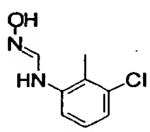
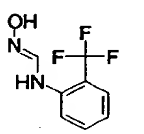
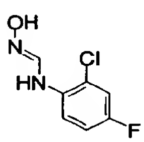
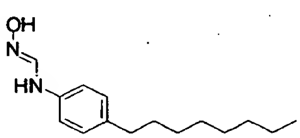
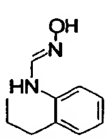
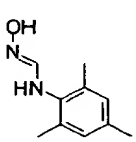
Comp. 19		144.0 – 145.0	181		179		0.08	Si02	Hexane :AcOEt =2:1	88.0	337.6
Comp. 20		149.0 – 150.0	181		179		0.07	Si02	Hexane :AcOEt =2:1	97.5	227.6
Comp. 21		115.5 – 116.5	165		163		0.14	Si02	Hexane :AcOEt =2:1	81.1	
Comp. 22		139.0 – 141.0					0.16	Si02	Hexane :AcOEt =2:1	95.7	
Comp. 23		110.0 – 111.5	171		169		0.12	Si02	Hexane :AcOEt =2:1	82.8	475.8
Comp. 24		119.0 – 120.5	205				0.10	Si02	Hexane :AcOEt =2:1	89.2	519.7
Comp. 25		142.5 – 144.5	189		187		0.15	Si02	Hexane :AcOEt =2:1	87.0	
Comp. 26		155.0 – 156.5	201		199		0.18	Si02	Hexane :AcOEt =2:1	86.0	203.7
Comp. 27		140.5 – 142.0	205		203		0.10	Si02	Hexane :AcOEt =2:1	103.3	1.7

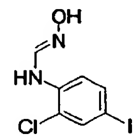
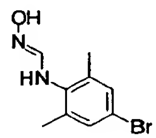
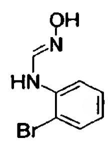
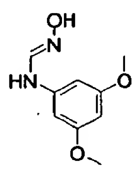
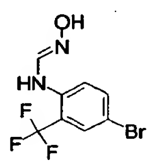
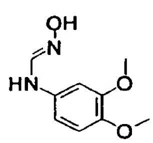
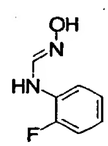
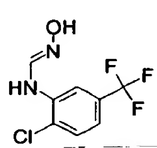
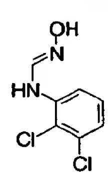
Comp. 28		119.0 – 120.5	235		233		0.15	Si02	Hexane :AcOEt =2:1	92.5	4.7
Comp. 29		93.0– 94.5	179		177		0.13	Si02	Hexane :AcOEt =2:1	93.6	
Comp. 30		143.0 – 143.5	179		177		0.12	Si02	Hexane :AcOEt =2:1	103.0	2.4
Comp. 31		131.0 – 132.0	179				0.12	Si02	Hexane :AcOEt =2:1	97.8	6.6
Comp. 32		114.0 – 115.0	179				0.16	Si02	Hexane :AcOEt =2:1	87.2	
Comp. 33		171.0			291		0.23	Si02	Hexane :AcOEt =2:1	91.9	
Comp. 34		163.0 – 163.5	293		291		0.17	Si02	Hexane :AcOEt =2:1	90.6	79.7
Comp. 35		161.0					0.17	Si02	Hexane :AcOEt =2:1	95.4	86.5
Comp. 36		163.0 – 164.0	215		213		0.10	Si02	Hexane :AcOEt =2:1	98.3	136.5

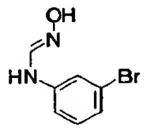
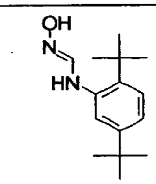
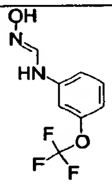
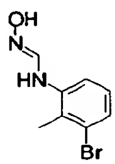
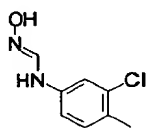
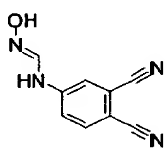
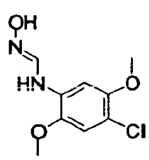
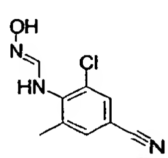
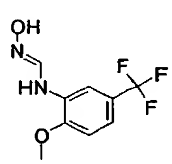
Comp. 37		167.0 – 167.5	195		193		0.06	Si02	Hexane :AcOEt =2:1	92.7	
Comp. 38		151.0 – 152.5	185		183		0.13	Si02	Hexane :AcOEt =2:1	89.8	79.8
Comp. 39		110.0 – 113.0	221		219		0.10	Si02	Hexane :AcOEt =2:1	99.0	22
Comp. 40		160.0 – 161.0	205		203		0.16	Si02	Hexane :AcOEt =2:1	98.2	
Comp. 41		161.0 – 161.5	229		227		0.13	Si02	Hexane :AcOEt =2:1	96.6	49.0
Comp. 42		144.0 – 145.0					0.44	Si02	CHCl3: MeOH= 9:1	99.9	
Comp. 43		123.0 – 124.0	169		167		0.30	Si02	CHCl3: MeOH= 9:1		168.1
Comp. 44		145.0 – 146.0	223		221		0.32	Si02	CHCl3: MeOH= 9:1		8.1
Comp. 45		163.5 – 164.5	243				0.45	Si02	CHCl3: MeOH= 9:1	53.5	

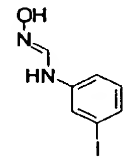
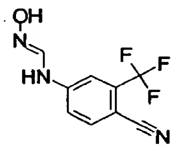
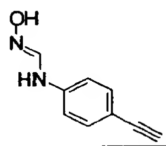
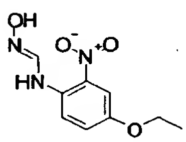
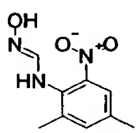
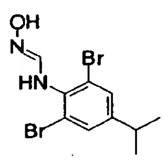
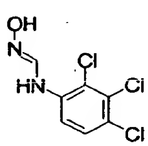
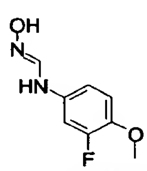
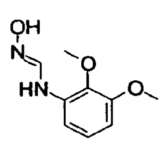
Comp. 46		100.5 – 102.0	205		203		0.24	Si02	CHCl3: MeOH= 9:1	48.5	355.3
Comp. 47		166.0 – 166.5	277		275		0.37	Si02	CHCl3: MeOH= 9:1	94.8	6.5
Comp. 48		155.0 – 156.0	335				0.52	Si02	CHCl3: MeOH= 9:1		
Comp. 49		122.5 – 124.0			271		0.44	Si02	CHCl3: MeOH= 9:1	46.7	
Comp. 50		155.5 – 156.5	173		171		0.34	Si02	CHCl3: MeOH= 9:1		25.5
Comp. 51		157.0 – 158.0	229		227		0.42	Si02	CHCl3: MeOH= 9:1	50.2	21.8
Comp. 52		145.0 – 146.0	181				0.43	Si02	CHCl3: MeOH= 9:1		
Comp. 53		159.0 – 160.0	271				0.66	Si02	CHCl3: MeOH= 9:1		
Comp. 54		162.5 – 163.5					0.43	Si02	CHCl3: MeOH= 9:1		

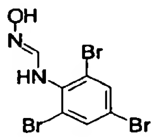
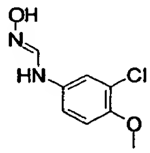
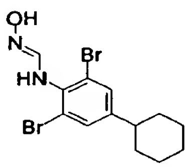
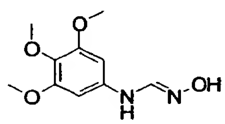
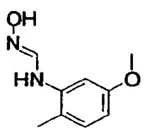
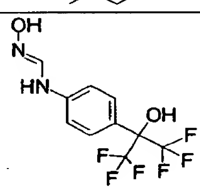
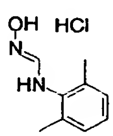
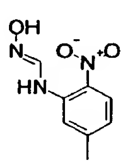
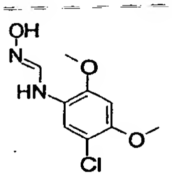
Comp. 55		130.5 – 132.0	277		275		0.5	Si02	CHCl3: MeOH= 9:1	31.3	
Comp. 56		144.0 – 145.5	190		188		0.42	Si02	CHCl3: MeOH= 9:1	50.6	
Comp. 57			193		191		0.22	Si02	Hexane :AcOEt =2:1	59.1	
Comp. 58		146.5 – 148.0	257		255		0.21	Si02	Hexane :AcOEt =2:1	99.9	7.1
Comp. 59			167		165		0.13	Si02	Hexane :AcOEt =2:1	49.0	
Comp. 60			181		179		0.15	Si02	Hexane :AcOEt =2:1		
Comp. 61					163		0.17	Si02	Hexane :AcOEt =2:1		
Comp. 62			151				0.12	Si02	Hexane :AcOEt =2:1	69.5	
Comp. 63			165		163		0.15	Si02	Hexane :AcOEt =2:1	49.3	

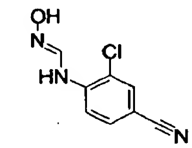
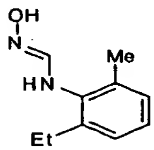
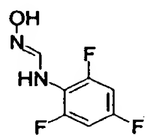
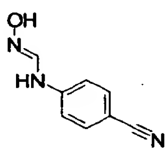
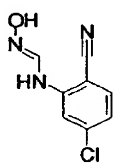
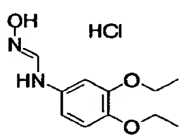
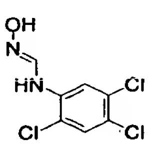
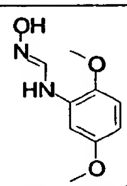
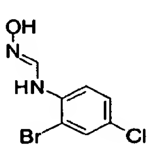
Comp. 64					163		0.13	Si02	Hexane :AcOEt =2:1		
Comp. 65			167		165		0.08	Si02	Hexane :AcOEt =2:1	59.3	
Comp. 66			181		179		0.10	Si02	Hexane :AcOEt =2:1	41.2	
Comp. 67			185		183		0.15	Si02	Hexane :AcOEt =2:1	48.4	
Comp. 68			205		203		0.15	Si02	Hexane :AcOEt =2:1		
Comp. 69			189		187		0.15	Si02	Hexane :AcOEt =2:1	58.7	
Comp. 70			249		247		0.15	Si02	Hexane :AcOEt =2:1	32.9	
Comp. 71			179		177		0.18	Si02	Hexane :AcOEt =2:1	42.5	
Comp. 72		168.0 – 169.0	179				0.12	Si02	Hexane :AcOEt =2:1	99.2	

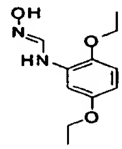
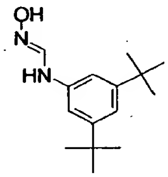
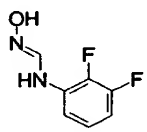
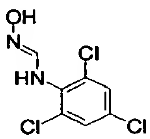
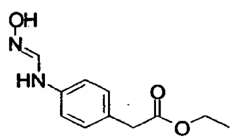
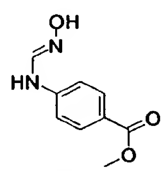
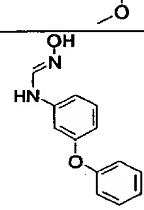
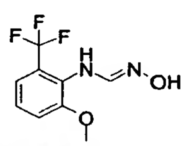
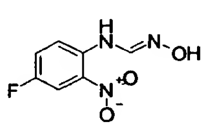
Comp. 73			297		295		0.18	Si02	Hexane :AcOEt =2:1	99.9	
Comp. 74			243		241		0.11	Si02	Hexane :AcOEt =2:1	43.7	
Comp. 75			215		213		0.16	Si02	Hexane :AcOEt =2:1	46.9	
Comp. 76					195		0.06	Si02	Hexane :AcOEt =2:1	35.1	
Comp. 77					281		0.17	Si02	Hexane :AcOEt =2:1	49.0	
Comp. 78			197		195		0.03	Si02	Hexane :AcOEt =2:1	36.3	
Comp. 79			155		153		0.15	Si02	Hexane :AcOEt =2:1	35.3	
Comp. 80			239		237		0.32	Si02	Hexane :AcOEt =2:1	37.2	
Comp. 81			205		203		0.14	Si02	Hexane :AcOEt =2:1	51.3	

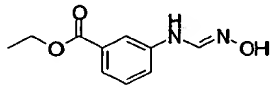
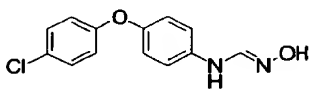
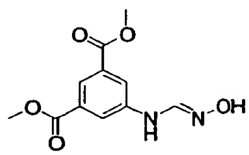
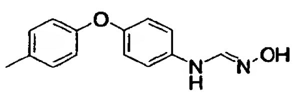
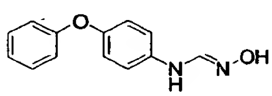
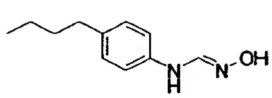
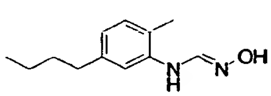
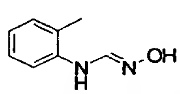
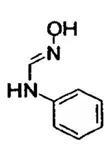
Comp. 82		133.5 – 134.5	215		213		0.12	Si02	Hexane :AcOEt =2:1	70.9	
Comp. 83			249				0.46	Si02	CHCl3: MeOH= 9:1		
Comp. 84			221		219		0.27	Si02	CHCl3: MeOH= 9:1		
Comp. 85			229		227		0.37	Si02	CHCl3: MeOH= 9:1		
Comp. 86			185		183		0.29	Si02	CHCl3: MeOH= 9:1	58.7	
Comp. 87			187				0.22	Si02	CHCl3: MeOH= 9:1		
Comp. 88			231		229		0.31	Si02	CHCl3: MeOH= 9:1		
Comp. 89			210		208		0.32	Si02	CHCl3: MeOH= 9:1		
Comp. 90			235				0.33	Si02	CHCl3: MeOH= 9:1	36.5	

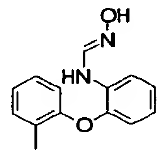
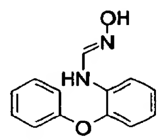
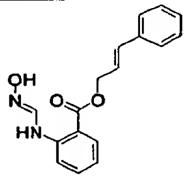
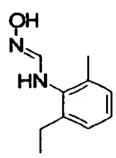
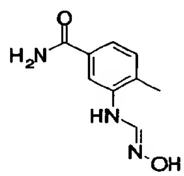
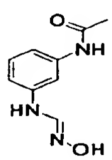
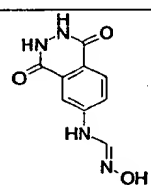
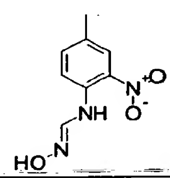
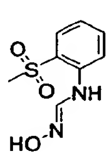
Comp. 91			263				0.27	Si02	CHCl3: MeOH= 9:1	36.6	
Comp. 92			230		228		0.51	Si02	CHCl3: MeOH= 9:1		
Comp. 93							0.21	Si02	CHCl3: MeOH= 9:1		
Comp. 94			226		224		0.29	Si02	CHCl3: MeOH= 9:1	41.2	
Comp. 95			210		208		0.32	Si02	CHCl3: MeOH= 9:1	44.5	
Comp. 96			335				0.40	Si02	CHCl3: MeOH= 9:1		
Comp. 97			239		237		0.32	Si02	CHCl3: MeOH= 9:1		
Comp. 98			185				0.21	Si02	CHCl3: MeOH= 9:1	43.9	
Comp. 99			197		195		0.29	Si02	CHCl3: MeOH= 9:1	40.8	

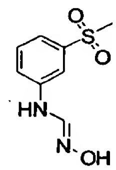
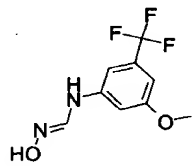
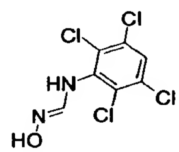
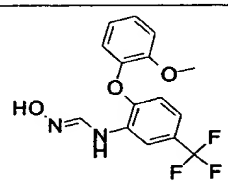
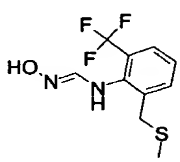
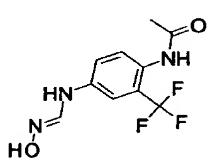
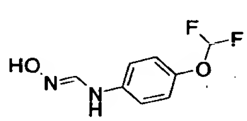
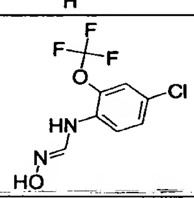
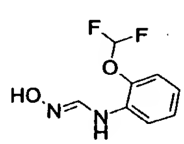
Comp. 100			370		368		0.38	Si02	CHCl3: MeOH= 9:1	44.3	
Comp. 101			201		199		0.24	Si02	CHCl3: MeOH= 9:1	52.4	
Comp. 102			375		373		0.41	Si02	CHCl3: MeOH= 9:1	44.4	
Comp. 103		143.0 – 146.0	227		225		0.21	Si02	CHCl3: MeOH= 9:1		
Comp. 104			181				0.39	Si02	CHCl3: MeOH= 9:1	31.9	
Comp. 105			303		301		0.12	Si02	CHCl3: MeOH= 9:1	46.7	
Comp. 106			165		163		0.25	Si02	CHCl3: MeOH= 9:1		
Comp. 107			196		194		0.37	Si02	CHCl3: MeOH= 9:1		
Comp. 108			231				0.39	Si02	CHCl3: MeOH= 9:1	36.4	

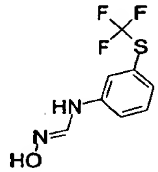
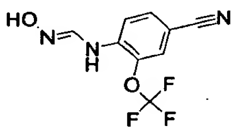
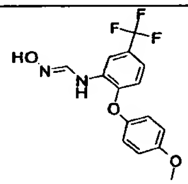
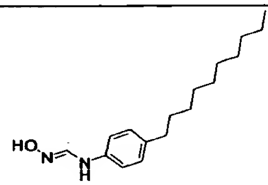
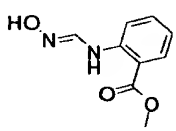
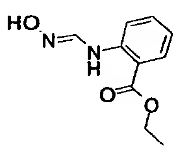
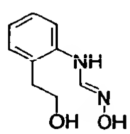
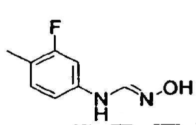
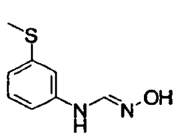
Comp. 109			196		194		0.13	Si02	CHCl3: MeOH= 9:1		
Comp. 110							0.13	Si02	CHCl3: MeOH= 9:1		
Comp. 111			191				0.37	Si02	CHCl3: MeOH= 9:1		
Comp. 112					160		0.24	Si02	CHCl3: MeOH= 9:1	37.4	
Comp. 113			196		194		0.08	Si02	CHCl3: MeOH= 9:1		
Comp. 114					223		0.21	Si02	CHCl3: MeOH= 9:1		
Comp. 115			239		237		0.4	Si02	CHCl3: MeOH= 9:1		
Comp. 116			197		195		0.37	Si02	CHCl3: MeOH= 9:1		
Comp. 117			249		247		0.39	Si02	CHCl3: MeOH= 9:1	71.6	

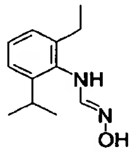
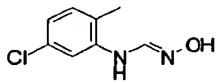
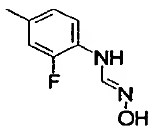
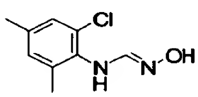
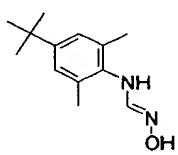
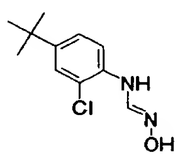
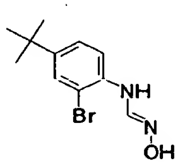
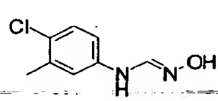
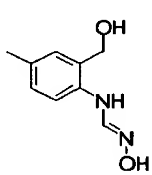
Comp. 118			225		223		0.41	Si02	CHCl3: MeOH= 9:1		
Comp. 119			249				0.27	Si02	CHCl3: MeOH= 9:1		
Comp. 120			173		171		0.37	Si02	CHCl3: MeOH= 9:1		
Comp. 121		166.5 – 167.0			237		0.29	Si02	EtOAc: hexane =1:2	72.0	
Comp. 122		106.0 – 107.5	223		221		0.05	Si02	EtOAc: hexane =1:2	94.7	28.9
Comp. 123		167.0 – 167.5		195	193		0.47	Si02 (NH)	EtOAc: MeOH =95:5	92.7	
Comp. 124		100.0 – 102.0			227		0.12	Si02	EtOAc: hexane =1:2	92.2	354.5
Comp. 125		138.0 – 139.5 (dec.)								67.6	
Comp. 126		172.5 – 173.0 (dec.)								34.9	

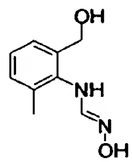
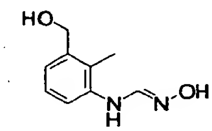
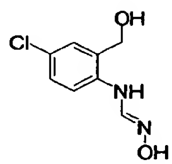
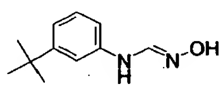
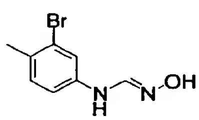
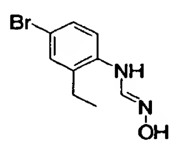
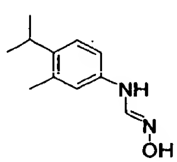
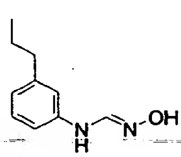
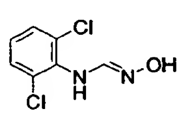
Comp. 127		137.5 – 138.5		209		207	0.53	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 128		143.0 – 145.0	263				0.26	Si02	CHCl3: MeOH =9:1	102.0	7.0
Comp. 129		183.0 – 183.5		253	251		0.50	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 130		155.0 – 156.0	243		241		0.10	Si02	EtOAc: hexane =1:2	116.5	6.9
Comp. 131		144.0 – 145.5	229		227		0.09	Si02	EtOAc: hexane =1:2	89.2	26
Comp. 132		122.0 – 123.5								117.6	3.9
Comp. 133		116.5 – 117.5								48.6	720
Comp. 134		154.0 – 154.5								57.4	3625
Comp. 135			137		135		0.10	Si02	EtOAc: hexane =1:2	49.3	

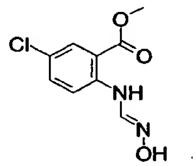
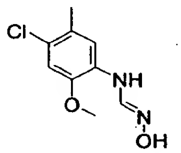
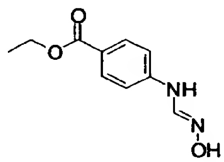
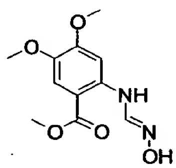
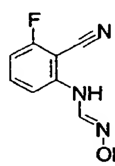
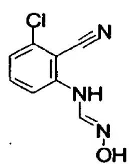
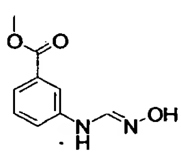
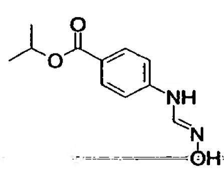
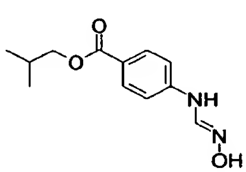
Comp. 136			243		241		0.17	Si02	EtOAc: hexane =1:2		
Comp. 137			229		227		0.15	Si02	EtOAc: hexane =1:2		
Comp. 138			297		295		0.11	Si02	EtOAc: hexane =1:2	44.0	
Comp. 139			179		177		0.13	Si02	EtOAc: hexane =1:2	69.7	
Comp. 140				194	192		0.23	Si02 (NH)	AcOEt: EtOH =90:10		
Comp. 141				194	192		0.06	Si02	CHCl3: MeOH =95:5		
Comp. 142					219		0.22	Si02	AcOEt: EtOH =90:10		
Comp. 143				196	194		0.25	Si02	CHCl3: MeOH =95:5	37.3	
Comp. 144				215	213		0.13	Si02	CHCl3: MeOH =95:5		

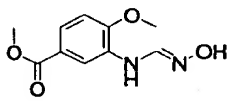
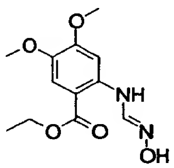
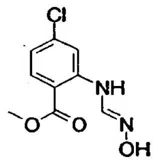
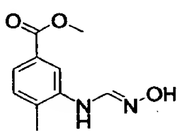
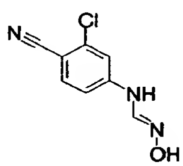
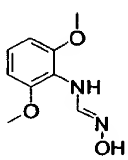
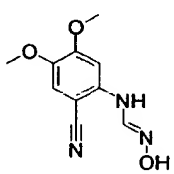
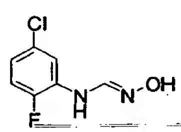
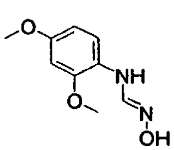
Comp. 145					213		0.11	Si02	CHCl3: MeOH =95:5		
Comp. 146				235	233		0.25	Si02 (NH)	AcOEt		
Comp. 147				273	271		0.26	Si02 (NH)	AcOEt		
Comp. 148				327	325		0.32	Si02 (NH)	AcOEt		
Comp. 149				265	263		0.34	Si02 (NH)	AcOEt	36.5	
Comp. 150				262	260		0.15	Si02 (NH)	AcOEt	34.1	
Comp. 151				203	201		0.20	Si02 (NH)	AcOEt	108.2	
Comp. 152				255	253		0.28	Si02 (NH)	AcOEt		
Comp. 153				203	201		0.29	Si02 (NH)	AcOEt	39.4	

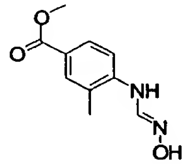
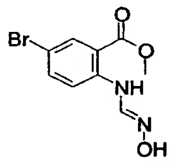
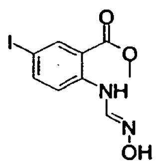
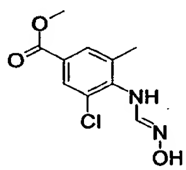
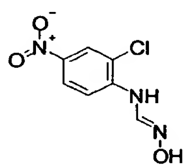
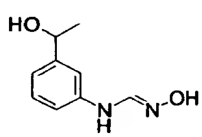
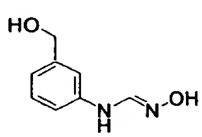
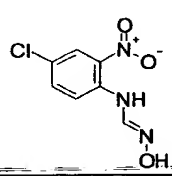
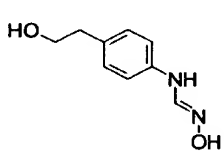
Comp. 154				237	235		0.24	Si02 (NH)	AcOEt		
Comp. 155				246	244		0.23	Si02 (NH)	AcOEt		
Comp. 156				327	325		0.32	Si02 (NH)	AcOEt	39.4	
Comp. 157				277	275		0.28	Si02 (NH)	AcOEt	121.4	
Comp. 158				195	193		0.24	Si02 (NH)	AcOEt		
Comp. 159				209	207		0.26	Si02 (NH)	AcOEt		
Comp. 160				181	179		0.21	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 161		156.0 – 157.0		169		167	0.51	Si02 (NH)	EtOAc: MeOH =95:5	88.6	13.4
Comp. 162				183	181		0.49	Si02 (NH)	EtOAc: MeOH =95:5	62.6	

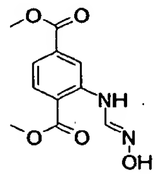
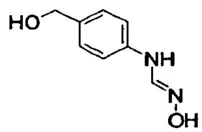
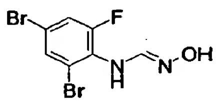
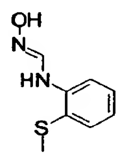
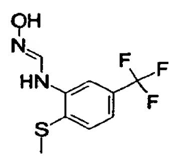
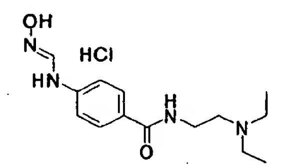
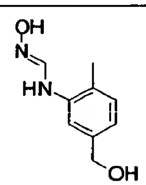
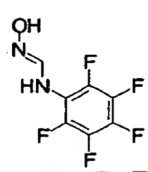
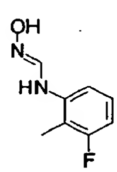
Comp. 163				207		205	0.61	Si02 (NH)	EtOAc: MeOH =95:5	40.0	
Comp. 164				186		184	0.55	Si02 (NH)	EtOAc: MeOH =95:5	86.7	
Comp. 165				169			0.54	Si02 (NH)	EtOAc: MeOH =95:5	105.7	
Comp. 166				200			0.56	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 167				221		219	0.58	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 168				228	226		0.57	Si02 (NH)	EtOAc: MeOH =95:5	61.9	
Comp. 169				272	270		0.57	Si02 (NH)	EtOAc: MeOH =95:5	104.1	
Comp. 170				186		184	0.50	Si02 (NH)	EtOAc: MeOH =95:5	99.8	
Comp. 171				181			0.23	Si02 (NH)	EtOAc: MeOH =95:5	54.1	

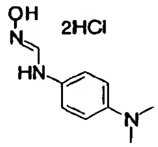
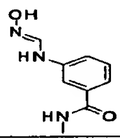
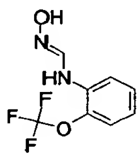
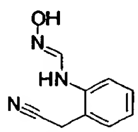
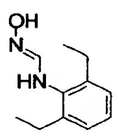
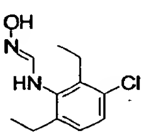
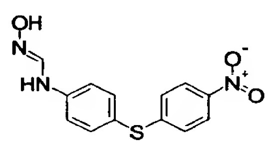
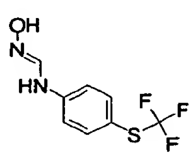
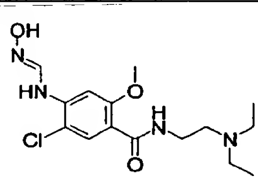
Comp. 172				181			0.21	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 173				181		179	0.30	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 174				202			0.22	Si02 (NH)	EtOAc: MeOH =95:5	62.4	
Comp. 175				193		191	0.56	Si02 (NH)	EtOAc: MeOH =95:5	69.9	
Comp. 176				230		228	0.51	Si02 (NH)	EtOAc: MeOH =95:5	67.0	
Comp. 177				244	242		0.53	Si02 (NH)	EtOAc: MeOH =95:5	85.4	
Comp. 178		121.0 – 122.5		193		191	0.52	Si02 (NH)	EtOAc: MeOH =95:5	91.4	9.0
Comp. 179				179		177	0.54	Si02 (NH)	EtOAc: MeOH =95:5	63.5	
Comp. 180				206	204		0.59	Si02 (NH)	EtOAc: MeOH =95:5		

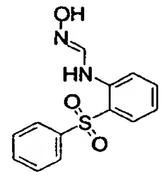
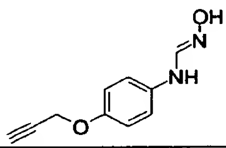
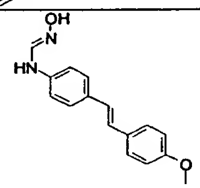
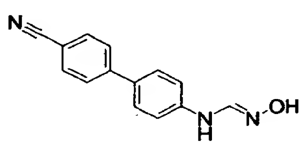
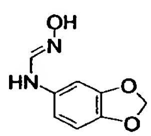
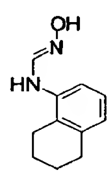
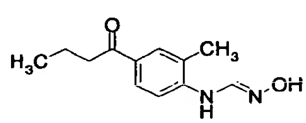
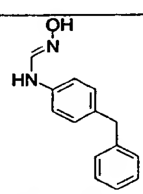
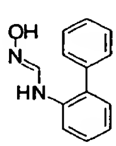
Comp. 181					227		0.54	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 182				216	214		0.56	Si02 (NH)	EtOAc: MeOH =95:5	90.2	
Comp. 183				209	207		0.50	Si02 (NH)	EtOAc: MeOH =95:5	92.0	
Comp. 184				255	253		0.48	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 185				180	178		0.36	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 186				197	195		0.29	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 187				195	193		0.50	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 188				223	221		0.50	Si02 (NH)	EtOAc: MeOH =95:5	59.1	
Comp. 189				237	235		0.50	Si02 (NH)	EtOAc: MeOH =95:5	116.8	

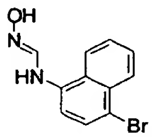
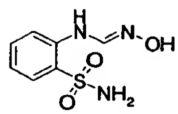
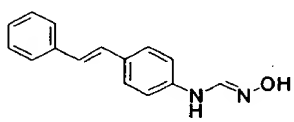
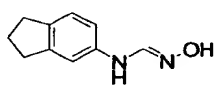
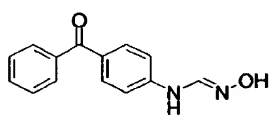
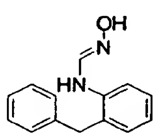
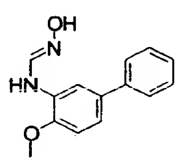
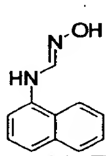
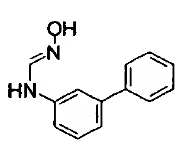
Comp. 190				225	223		0.51	Si02 (NH)	EtOAc: MeOH =95:5	44.9	
Comp. 191				269	267		0.50	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 192				230	228		0.56	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 193				209		207	0.52	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 194				197		195	0.44	Si02 (NH)	EtOAc: MeOH =95:5	67.5	
Comp. 195				197			0.51	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 196						220	0.52	Si02 (NH)	EtOAc: MeOH =95:5	46.9	
Comp. 197				190	188		0.57	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 198				197			0.50	Si02 (NH)	EtOAc: MeOH =95:5	81.8	

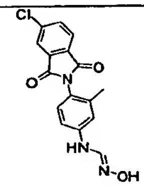
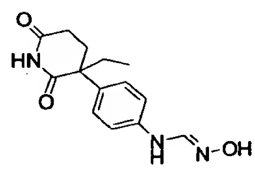
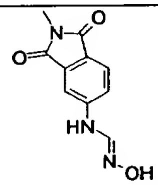
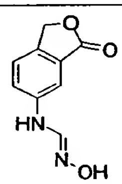
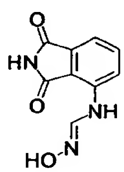
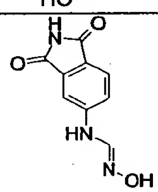
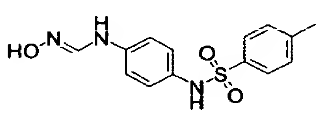
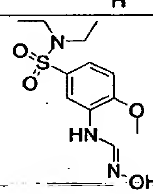
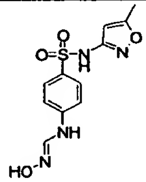
Comp. 199				209	207		0.50	Si02 (NH)	EtOAc: MeOH =95:5	85.6	
Comp. 200				274	272		0.50	Si02 (NH)	EtOAc: MeOH =95:5	53.3	
Comp. 201				321	319		0.50	Si02 (NH)	EtOAc: MeOH =95:5	70.1	
Comp. 202				244	242		0.53	Si02 (NH)	EtOAc: MeOH =95:5	31.6	
Comp. 203				217		215	0.45	Si02 (NH)	EtOAc: MeOH =95:5	51.1	
Comp. 204				181		179	0.30	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 205				167		165	0.25	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 206				217			0.49	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 207		138.0 – 140.0		181		179	0.29	Si02 (NH)	EtOAc: MeOH =95:5	90.7	11.6

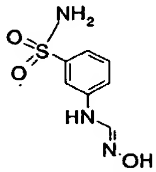
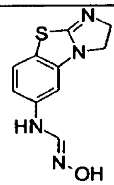
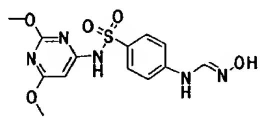
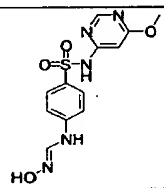
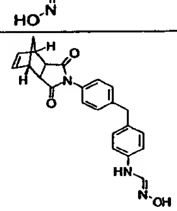
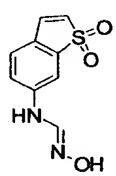
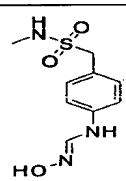
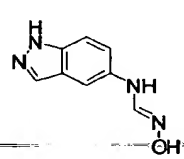
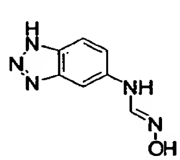
Comp. 208				253	251		0.53	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 209		169.5 – 170.0		167	165		0.27	Si02 (NH)	EtOAc: MeOH =95:5	102.2	151.6
Comp. 210				313	311		0.58	Si02 (NH)	EtOAc: MeOH =95:5	78	
Comp. 211			183		181		0.35	Si02	CHCl3: MeOH =9:1		
Comp. 212			251		249		0.35	Si02	CHCl3: MeOH =9:1		
Comp. 213			279				0.15	Si02	CHCl3: MeOH =9:1		
Comp. 214			181		179		0.12	Si02	CHCl3: MeOH =9:1	31.9	
Comp. 215					225		0.25	Si02	CHCl3: MeOH =9:1	36.1	
Comp. 216					167		0.31	Si02	CHCl3: MeOH =9:1		

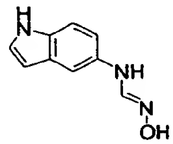
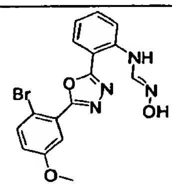
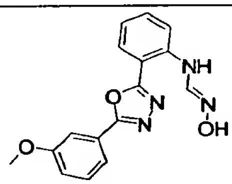
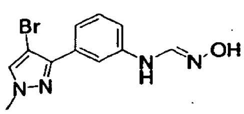
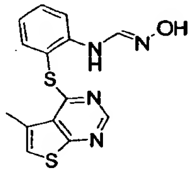
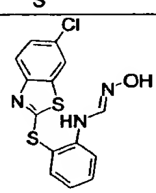
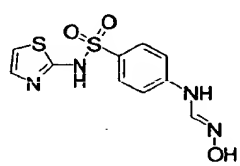
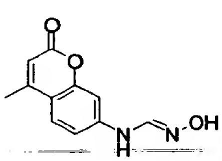
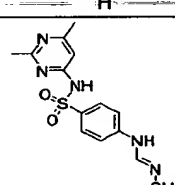
Comp. 217			253				0.4	Si02	CHCl3: MeOH =9:1		
Comp. 218			194				0.08	Si02	CHCl3: MeOH =9:1		
Comp. 219			221		219		0.38	Si02	CHCl3: MeOH =9:1		
Comp. 220			176		174		0.28	Si02	CHCl3: MeOH =9:1		
Comp. 221			193		191		0.35	Si02	CHCl3: MeOH =9:1		
Comp. 222					225		0.29	Si02	CHCl3: MeOH =9:1		
Comp. 223			290		288		0.34	Si02	CHCl3: MeOH =9:1	52.2	
Comp. 224			237		235		0.31	Si02	CHCl3: MeOH =9:1	47.1	
Comp. 225			343		341		0.05	Si02	CHCl3: MeOH =9:1		

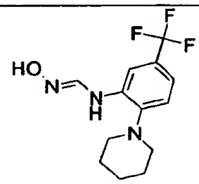
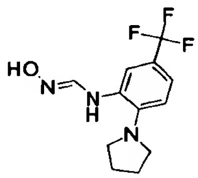
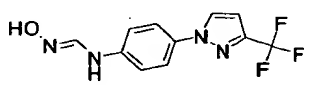
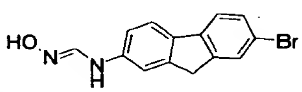
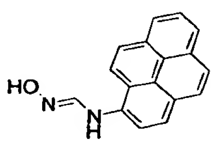
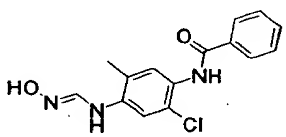
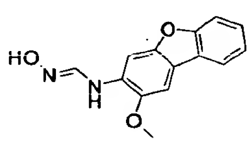
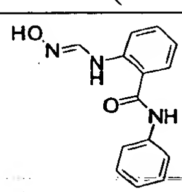
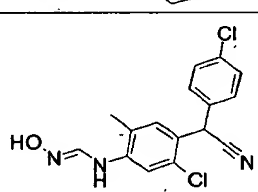
Comp. 226			277		275		0.37	Si02	CHCl3: MeOH =9:1		
Comp. 227		139.0 – 141.0	191		189		0.31	Si02	AcOEt	117.8	39.7
Comp. 228					267		0.15	Si02	EtOAc: hexane =1:2	72.0	
Comp. 229		194.0 – 195.0	238		236		0.34	Si02	CHCl3: MeOH =9:1	99.3	16.0
Comp. 230		165.0 – 165.5	181		179		0.07	Si02	EtOAc: hexane =1:2		
Comp. 231		168.5 – 169.0	191		189		0.16	Si02	EtOAc: hexane =1:2	92.9	196.5
Comp. 232		154.0 – 155.0								86.0	6.6
Comp. 233		118.0 – 119.5	227		225		0.10	Si02	EtOAc: hexane =1:2	87.5	51.9
Comp. 234		111.0 – 113.0	213		211		0.15	Si02	EtOAc: hexane =1:2	74.1	

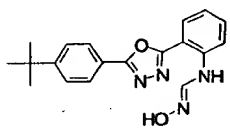
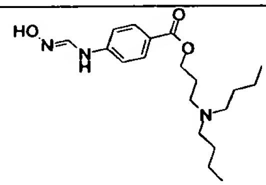
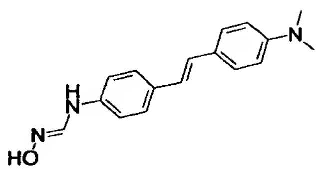
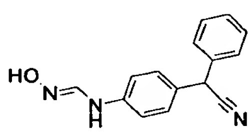
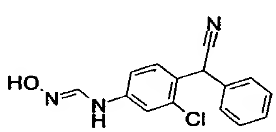
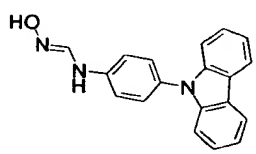
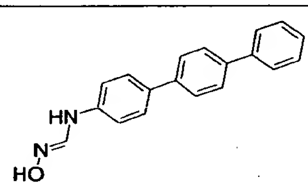
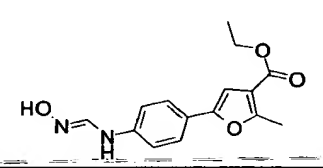
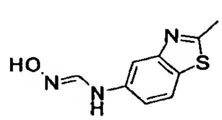
Comp. 235		167.5 – 168.0			263		0.13	Si02	EtOAc: hexane =1:2	77.8	5915.9
Comp. 236		130.5 – 131.5									
Comp. 237		197.5 – 198.0			237		0.17	Si02	EtOAc: hexane = 1:2	96.6	26.2
Comp. 238		142.5 – 144.0	177		175		0.12	Si02	EtOAc: hexane =1:2	101.6	30.0
Comp. 239		182.5 – 183.0									4078
Comp. 240			227		225		0.15	Si02	EtOAc: hexane =1:2		
Comp. 241			243				0.15	Si02	EtOAc: hexane =1:2		
Comp. 242			187		185		0.13	Si02	EtOAc: hexane =1:2	50.6	
Comp. 243			213		211		0.11	Si02	EtOAc: hexane =1:2		

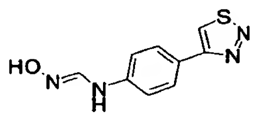
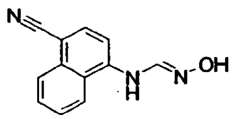
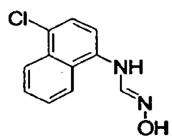
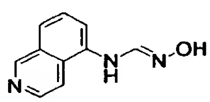
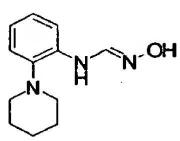
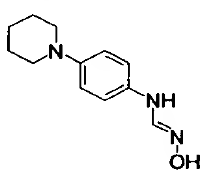
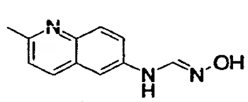
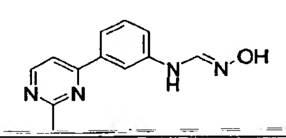
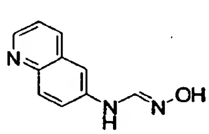
Comp. 244				330	328	328	0.49	Si02	CHCl3: MeOH =95:5	32.7	
Comp. 245				276	274	274	0.38	Si02 (NH)	AcOEt: EtOH =90:10	55.4	
Comp. 246				220	218	218	0.22	Si02	CHCl3: MeOH =95:5		
Comp. 247				193	191	191	0.15	Si02	CHCl3: MeOH =95:5		
Comp. 248				206	204		0.64	Si02	AcOEt: EtOH =90:10		
Comp. 249				206	204		0.6	Si02	AcOEt: EtOH =90:10		
Comp. 250				306	304	304	0.3	Si02 (NH)	AcOEt: EtOH =90:10		
Comp. 251				302	300	300	0.3	Si02	CHCl3: MeOH =95:5		
Comp. 252					295		0.24	Si02	CHCl3: MeOH =95:5		

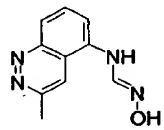
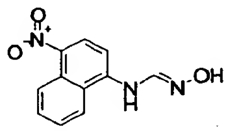
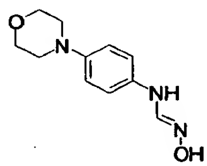
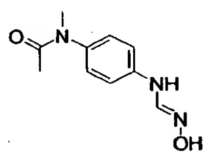
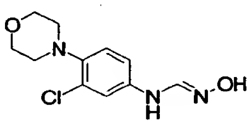
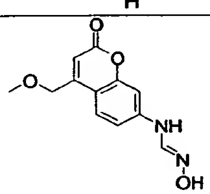
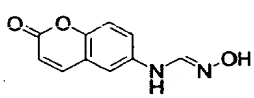
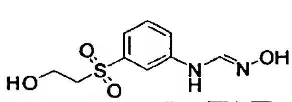
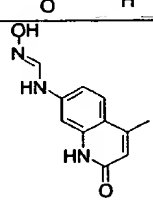
Comp. 253				216	214	214	0.27	Si02 (NH)	AcOEt: EtOH =90:10		
Comp. 254					233		0.56	Si02 (NH)	AcOEt: EtOH =90:10		
Comp. 255				354	352	352	0.57	Si02	AcOEt: EtOH =90:10		
Comp. 256					321		0.28	Si02	CHCl3: MeOH =95:5		
Comp. 257				388	386	386	0.15	Si02	CHCl3: MeOH =95:5		
Comp. 258				225	223	223	0.08	Si02	CHCl3: MeOH =95:5		
Comp. 259				244	242		0.33	Si02 (NH)	AcOEt: EtOH =90:10	52.8	
Comp. 260				177	175	175	0.21	Si02	CHCl3: MeOH =95:5		
Comp. 261				178	176	176	0.04	Si02	CHCl3: MeOH =95:5		

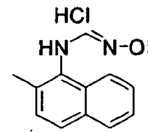
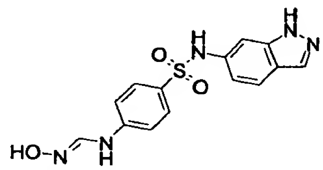
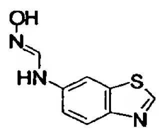
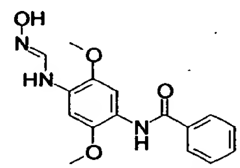
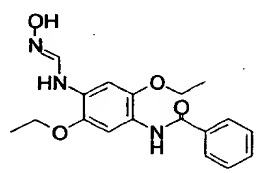
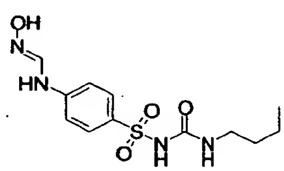
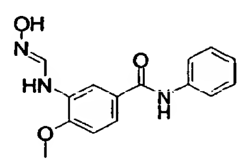
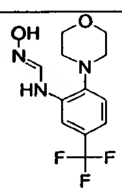
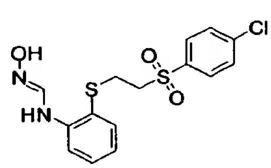
Comp. 262				176		174	0.03	Si02	CHCl3: MeOH =95:5		
Comp. 263				389	387	387	0.26	Si02	CHCl3: MeOH =95:5		
Comp. 264				311	309	309	0.25	Si02	CHCl3: MeOH =95:5		
Comp. 265				295		293	0.19	Si02	CHCl3: MeOH =95:5		
Comp. 266				317	315		0.24	Si02	CHCl3: MeOH =95:5		
Comp. 267					334		0.31	Si02	CHCl3: MeOH =95:5		
Comp. 268				299	297	297	0.05	Si02	CHCl3: MeOH =95:5		
Comp. 269				219	217	217	0.17	Si02	CHCl3: MeOH =95:5		
Comp. 270				322	320	320	0.05	Si02	CHCl3: MeOH =95:5		

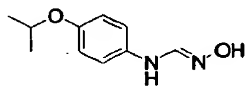
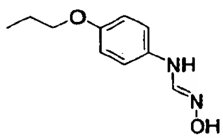
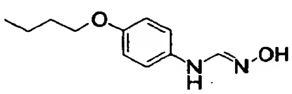
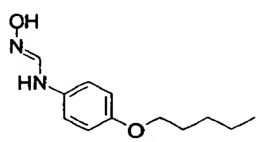
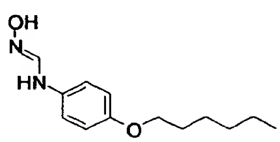
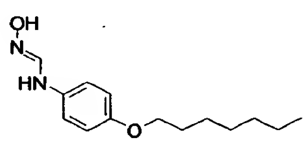
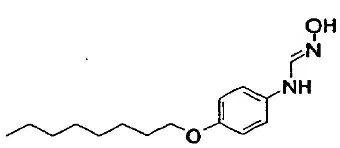
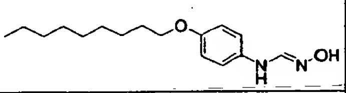
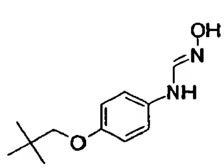
Comp. 271				288	286	286	0.37	Si02 (NH)	AcOEt		
Comp. 272				274	272	272	0.33	Si02 (NH)	AcOEt		
Comp. 273		165.0 – 167.0		271	269	269	0.20	Si02 (NH)	AcOEt	89.2	96.8
Comp. 274				303	301	301	0.16	Si02 (NH)	AcOEt	94.5	
Comp. 275				261	259	259	0.16	Si02 (NH)	AcOEt		
Comp. 276		207.0 – 207.5		304	302	302	0.16	Si02 (NH)	AcOEt	71.8	55.9
Comp. 277				257	255	255	0.22	Si02 (NH)	AcOEt	76.4	
Comp. 278				256	254		0.15	Si02 (NH)	AcOEt	65.3	
Comp. 279				334	332	332	0.21	Si02 (NH)	AcOEt	42.8	

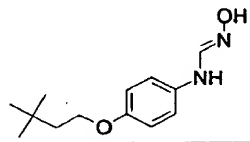
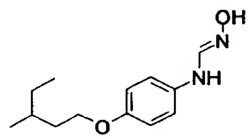
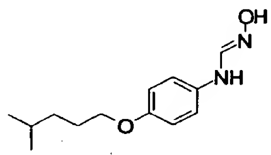
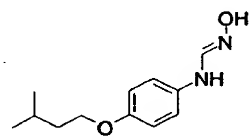
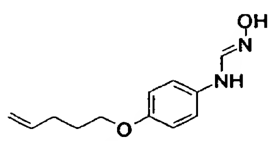
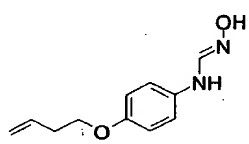
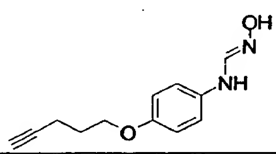
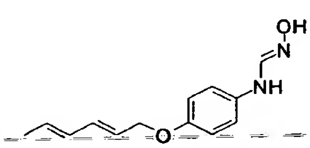
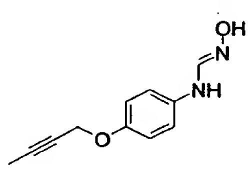
Comp. 280				337	335	335	0.21	Si02 (NH)	AcOEt		
Comp. 281				350	348	348	0.21	Si02 (NH)	AcOEt	50.9	
Comp. 282				282		280	0.17	Si02 (NH)	AcOEt	122.9	
Comp. 283				252	250	250	0.16	Si02 (NH)	AcOEt	62.6	
Comp. 284				286	284	284	0.16	Si02 (NH)	AcOEt		
Comp. 285				302	300	300	0.16	Si02 (NH)	AcOEt		
Comp. 286				289	287	287	0.16	Si02 (NH)	AcOEt		
Comp. 287				289	287	287	0.17	Si02 (NH)	AcOEt		
Comp. 288				208	206	206	0.14	Si02 (NH)	AcOEt		

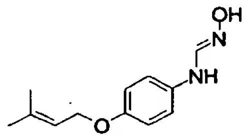
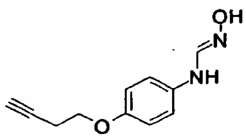
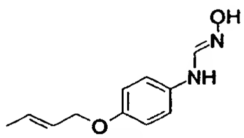
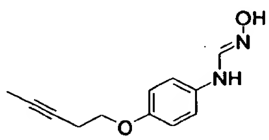
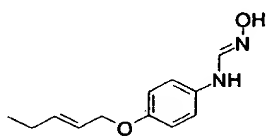
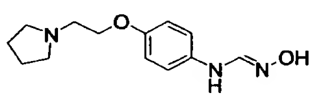
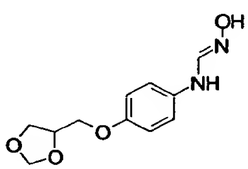
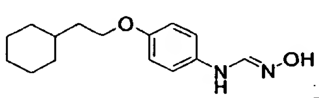
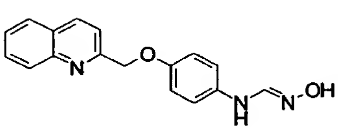
Comp. 289				221	219	219	0.13	Si02 (NH)	AcOEt		
Comp. 290				212	210	210	0.42	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 291				222	220	220	0.48	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 292				188	186	186	0.36	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 293				220	218	218	0.59	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 294		162.0 – 162.5		220		218	0.47	Si02 (NH)	EtOAc: MeOH =95:5	103.2	4.9
Comp. 295				202		200	0.37	Si02 (NH)	EtOAc: MeOH =95:5	73.8	
Comp. 296				229		227	0.41	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 297				188		186	0.35	Si02 (NH)	EtOAc: MeOH =95:5	71.1	

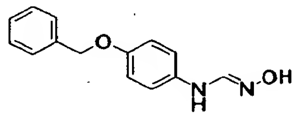
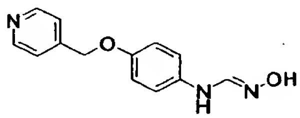
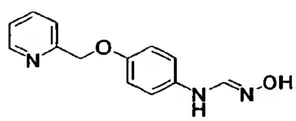
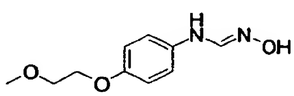
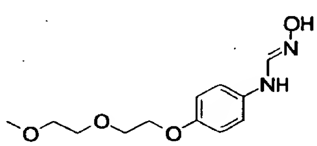
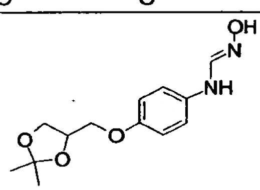
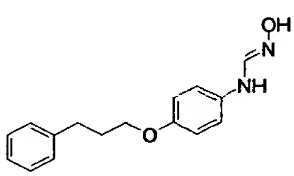
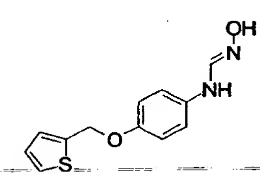
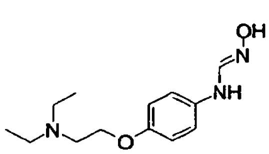
Comp. 298				203		201	0.33	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 299				232	230	230	0.40	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 300		182.0 – 182.5		222		220	0.44	Si02 (NH)	EtOAc: MeOH =95:5	96.3	5.7
Comp. 301				208		206	0.36	Si02 (NH)	EtOAc: MeOH =95:5	62.1	
Comp. 302		177.5 – 178.0		257		255	0.47	Si02 (NH)	EtOAc: MeOH =95:5	96.5	1.9
Comp. 303				249	247	247	0.35	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 304				205	203		0.33	Si02 (NH)	EtOAc: MeOH =95:5	68.5	
Comp. 305				245		243	0.14	Si02 (NH)	EtOAc: MeOH =95:5		
Comp. 306					216		0.10	Si02	CHCl3: MeOH =9:1		

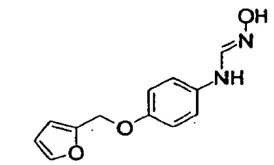
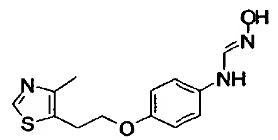
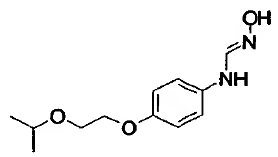
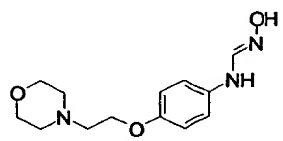
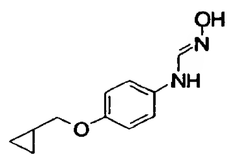
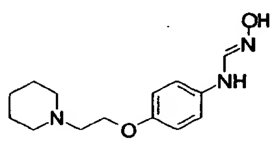
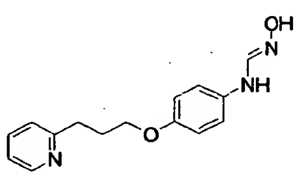
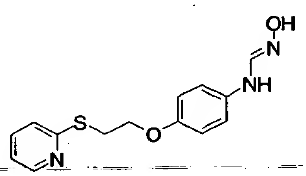
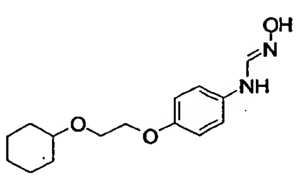
Comp. 307			201				0.40	Si02	CHCl3: MeOH =9:1		
Comp. 308			332		330		0.08	Si02	CHCl3: MeOH =9:1		
Comp. 309			194				0.17	Si02	CHCl3: MeOH =9:1		
Comp. 310			316		314		0.25	Si02	CHCl3: MeOH =9:1		
Comp. 311			344		342		0.25	Si02	CHCl3: MeOH =9:1		
Comp. 312			315				0.15	Si02	CHCl3: MeOH =9:1		
Comp. 313			286		284		0.25	Si02	CHCl3: MeOH =9:1		
Comp. 314			290				0.38	Si02	CHCl3: MeOH =9:1		
Comp. 315			371		369		0.48	Si02	CHCl3: MeOH =9:1	50.7	

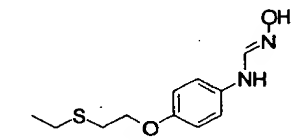
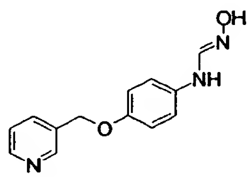
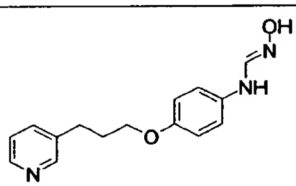
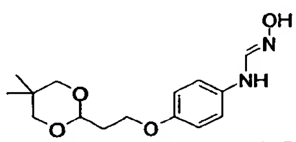
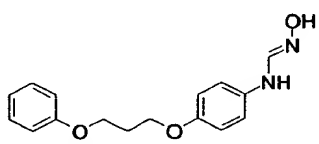
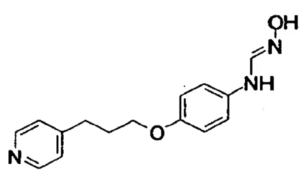
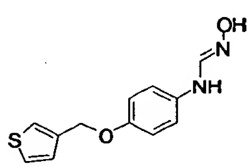
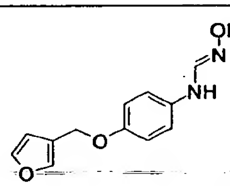
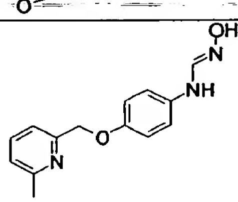
Comp. 316		144.0 – 146.0	195		193		0.09	Si02	Hexane : AcOEt =2:1	97.9	24.0
Comp. 317		132.0 – 133.0		195			0.51	SiO 2 (NH)	EtOAc: MeOH =95:5	93.8	3.5
Comp. 318		136.5 – 137.5	209		207		0.09	Si02	Hexane :AcOEt =2:1		9.9
Comp. 319		126.0 – 127.0	223		221		0.13	Si02	Hexane :AcOEt =2:1	99.9	3.8
Comp. 320		125.0 – 126.0	237		235		0.11	Si02	Hexane :AcOEt =2:1	92.5	1.3
Comp. 321		121– 122.5	251		249		0.36	SiO 2 (NH)	AcOEt	99.9	3.7
Comp. 322			265		263		0.36	SiO 2 (NH)	AcOEt	117.5	
Comp. 323		128.0 – 130.0	279		277		0.12	Si02	Hexane :AcOEt =2:1		25.9
Comp. 324		148.5 – 149.5	223		221		0.22	SiO 2	AcOEt	99	3.7

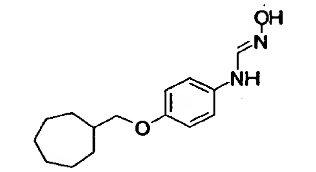
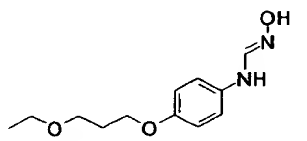
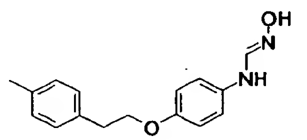
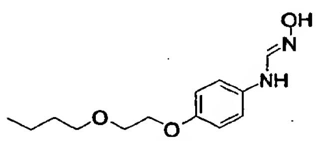
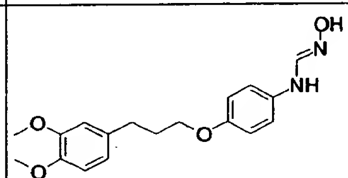
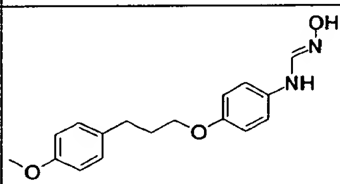
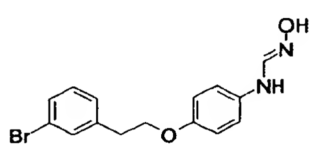
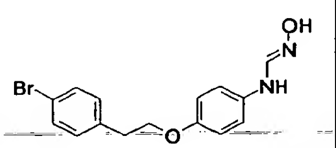
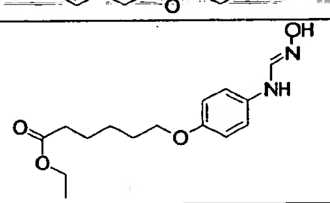
Comp. 325		123.0 – 125.0	237		235		0.23	SiO 2	AcOEt	106	2.6
Comp. 326			237		235		0.35	SiO 2 (NH)	AcOEt	110.8	
Comp. 327				237	235		0.35	SiO 2 (NH)	AcOEt	110.1	
Comp. 328			233		221		0.33	SiO 2 (NH)	AcOEt	121.4	
Comp. 329		127.0 – 128.0		221	219		0.33	SiO 2 (NH)	AcOEt	121.1	0.7
Comp. 330		122.0 – 124.0	207		205		0.33	SiO 2 (NH)	AcOEt	118.8	2.4
Comp. 331		139.0 – 139.5		219	217		0.31	SiO 2 (NH)	AcOEt	118.8	3.2
Comp. 332		169.5 – 170.0	233		231		0.31	SiO 2 (NH)	AcOEt	110.6	2.1
Comp. 333		171.5 – 172.0	205		203		0.3	SiO 2 (NH)	AcOEt	119.3	2.2

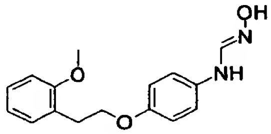
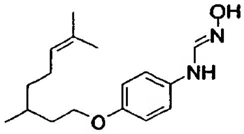
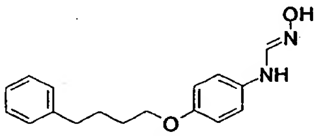
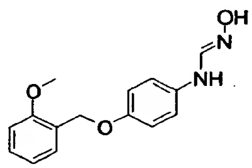
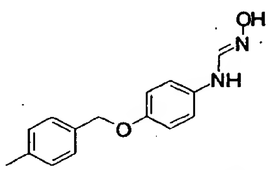
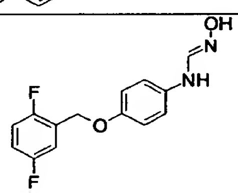
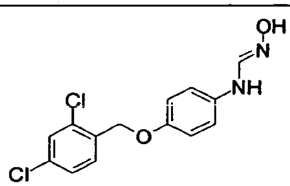
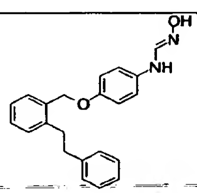
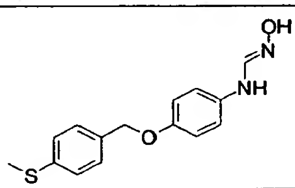
Comp. 334		125.0 – 126.0	221				0.23	SiO 2	AcOEt	105	3.2
Comp. 335		139.0 – 141.0	205				0.23	SiO 2	AcOEt	110	1.4
Comp. 336		142.5 – 146.0	207		205		0.31	SiO 2 (NH)	AcOEt	117.6	3.2
Comp. 337		135.0 – 136.5	219		217		0.31	SiO 2 (NH)	AcOEt	119.4	2.1
Comp. 338		100.0 – 102.0	221			219	0.33	SiO 2 (NH)	AcOEt	119.8	0.9
Comp. 339		113.5 – 114.5	250		248		0.11	SiO 2	AcOEt	88	124.2
Comp. 340		157.5 –158								97.4	3.0
Comp. 341		129.5 –133	263		261		0.23	SiO 2	AcOEt	104	1.2
Comp. 342		174.5 – 175.5								98.5	5.3

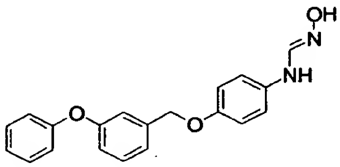
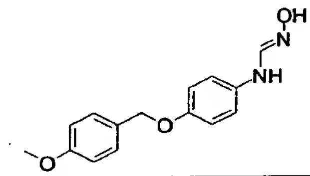
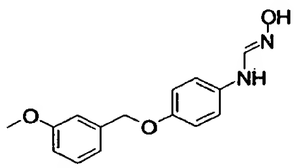
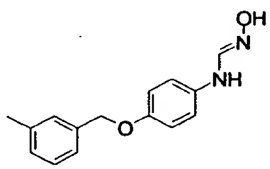
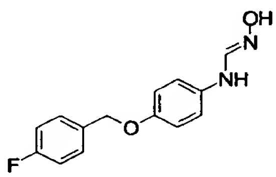
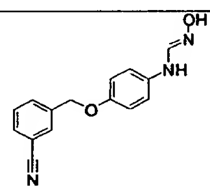
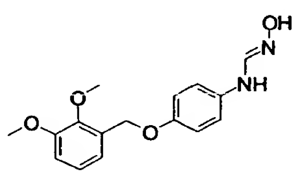
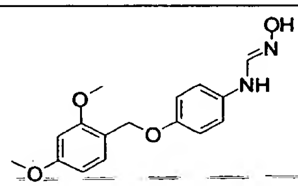
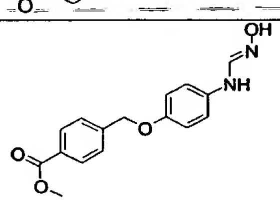
Comp. 343		166.5 – 167.0								84.5	3.3
Comp. 344		180– 180.5	244				0.12	SiO 2	AcOEt	107	37.5
Comp. 345		159.5 –161	244				0.14	SiO 2	AcOEt	101	23.1
Comp. 346		104.0 – 107.0								106.2	8.9
Comp. 347		80.5– 81.5	255		253		0.18	SiO 2	AcOEt	105	3.7
Comp. 348		128.5 – 129.5	267		265		0.21	SiO 2	AcOEt	103	3.4
Comp. 349		152.5 – 153.0	271		269		0.21	SiO 2	AcOEt	100	1.6
Comp. 350		168.0 – 168.5	249				0.19	SiO 2	AcOEt	91	1.4
Comp. 351			252		250		0.18	SiO 2	AcOEt	89	

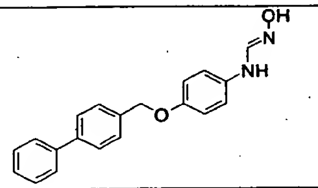
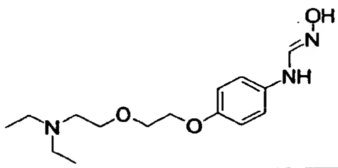
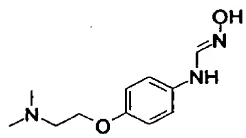
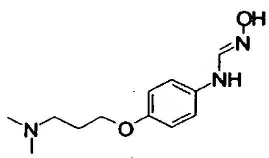
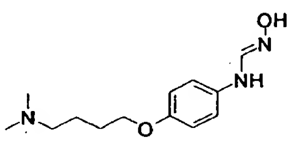
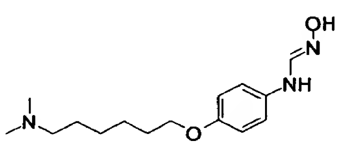
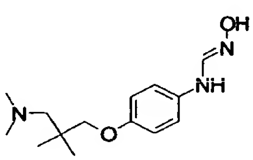
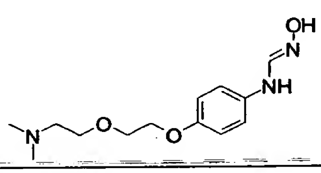
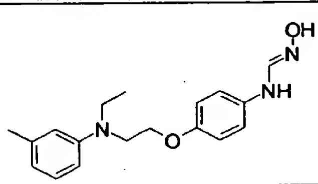
Comp. 352		158.5 – 159.5	233				0.2	SiO 2	AcOEt	97	4.6
Comp. 353		158.0 – 160.0	278		276		0.14	SiO 2	AcOEt	105	3.7
Comp. 354		113.0 – 114.0	239		237		0.23	SiO 2	AcOEt	106	3.0
Comp. 355		141.0 – 142.0	266		264		0.14	SiO 2	AcOEt	107	5.9
Comp. 356		141.0 – 142.5	207				0.23	SiO 2	AcOEt	102	2.6
Comp. 357			264		262		0.16	SiO 2	AcOEt	98	
Comp. 358		138.0 – 139.5	272		270		0.14	SiO 2	AcOEt	103	3.1
Comp. 359		132.5 – 134.5	290		288		0.2	SiO 2	AcOEt	102	1.4
Comp. 360			279		277		0.22	SiO 2	AcOEt		

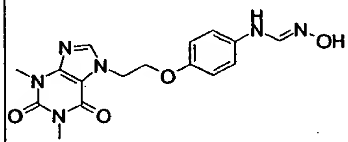
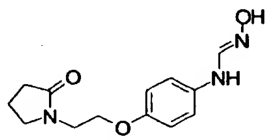
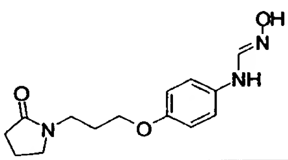
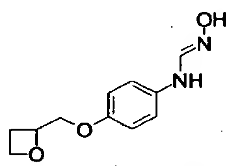
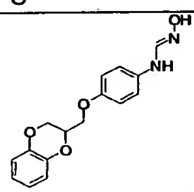
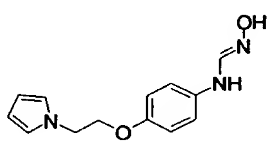
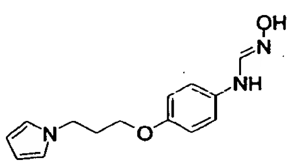
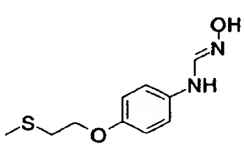
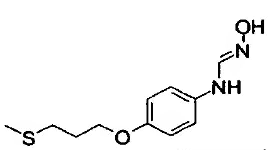
Comp. 361		104.0 – 106.0	241		239		0.22	SiO 2	AcOEt	106	2.1
Comp. 362		156.0 – 157.0	244				0.11	SiO 2	AcOEt	106	2.1
Comp. 363		154.0 – 155.0	272		270		0.11	SiO 2	AcOEt	105	0.78
Comp. 364		136.5 – 137.5	295		293		0.21	SiO 2	AcOEt	104	2.0
Comp. 365		143.5 – 145.0	287		285		0.19	SiO 2	AcOEt	105	1.4
Comp. 366		188.0 – 189.0	272				0.09	SiO 2	AcOEt	105	1.2
Comp. 367		165.0 – 166.0	249				0.18	SiO 2	AcOEt	103	2.1
Comp. 368		165.5 – 166.0	233				0.19	SiO 2	AcOEt	96	2.5
Comp. 369		146.5 – 149.0	258				0.16	SiO 2	AcOEt	105	3.1

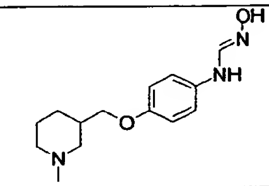
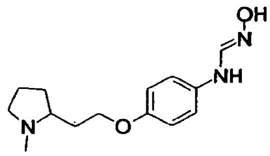
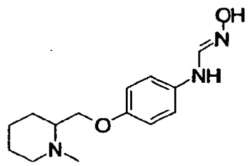
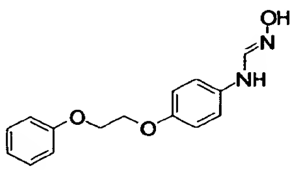
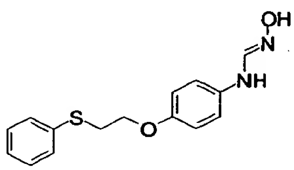
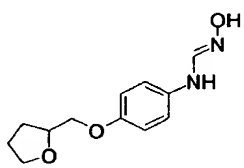
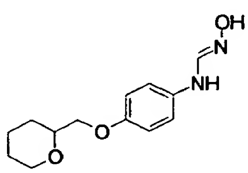
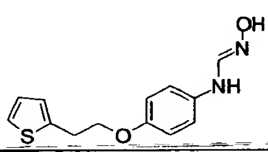
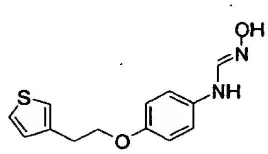
Comp. 370			263	263	261	261	0.33	SiO_2 (NH)	AcOEt	113.7	
Comp. 371		93.0–94.0	239	239	237	237	0.31	SiO_2 (NH)	AcOEt	110.4	0.9
Comp. 372				271	269	269	0.31	SiO_2 (NH)	AcOEt	100.5	
Comp. 373		97.0–99.0		253	251	251	0.31	SiO_2 (NH)	AcOEt	115.3	0.8
Comp. 374			331	331	329	329	0.3	SiO_2 (NH)	AcOEt	119.1	
Comp. 375				301	299	299	0.3	SiO_2 (NH)	AcOEt	117.7	
Comp. 376				336	333	334	0.3	SiO_2 (NH)	AcOEt	114.9	
Comp. 377				336	334	334	0.3	SiO_2 (NH)	AcOEt	107.4	
Comp. 378				295	293	293	0.3	SiO_2 (NH)	AcOEt	102.4	

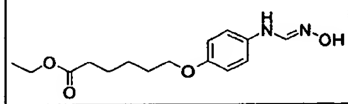
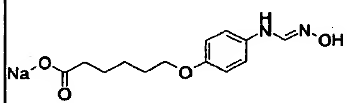
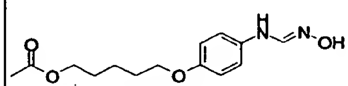
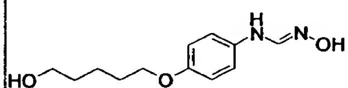
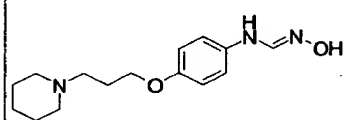
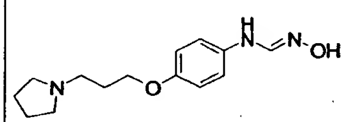
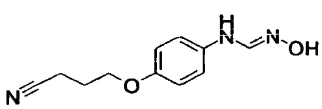
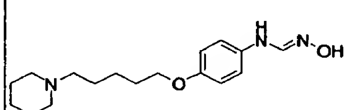
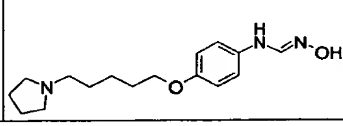
Comp. 379				287	285	285	0.27	SiO_2 (NH)	AcOEt	105.4	
Comp. 380				291	289	289	0.26	SiO_2 (NH)	AcOEt	118.9	
Comp. 381				285	283	283	0.27	SiO_2 (NH)	AcOEt	116.0	
Comp. 382		153.0 – 153.5		273			0.26	SiO_2 (NH)	AcOEt	122.5	3.1
Comp. 383				257	255	255	0.26	SiO_2 (NH)	AcOEt	116.2	
Comp. 384		167.0 – 167.5		279	277		0.27	SiO_2 (NH)	AcOEt	117.3	2.8
Comp. 385				312	310	310	0.27	SiO_2 (NH)	AcOEt	109.0	
Comp. 386				347	345		0.27	SiO_2 (NH)	AcOEt	105.2	
Comp. 387		163.0 – 164.0	289	289			0.27	SiO_2 (NH)	AcOEt	97.8	0.9

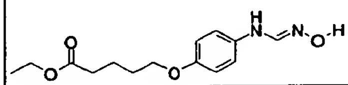
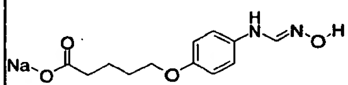
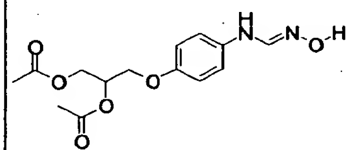
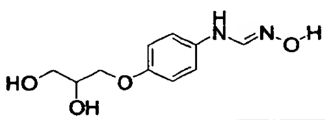
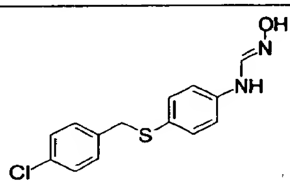
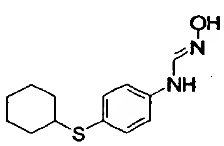
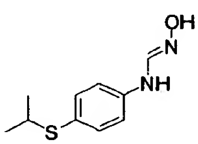
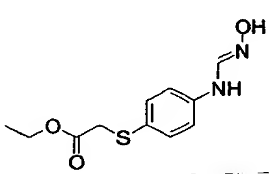
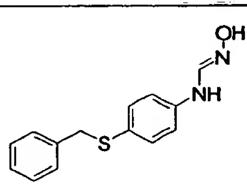
Comp. 388				335	333	333	0.27	SiO 2 (NH)	AcOEt	96.2	
Comp. 389		167.0 – 167.5		273		271	0.31	SiO 2 (NH)	AcOEt	105.5	1.6
Comp. 390		152.5 – 153.5		273		271	0.31	SiO 2 (NH)	AcOEt	112.8	2.7
Comp. 391		161.5 – 162.0		257	255	255	0.31	SiO 2 (NH)	AcOEt	113.4	2.4
Comp. 392		165.5 – 166.0	261	261	259		0.31	SiO 2 (NH)	AcOEt	109.6	2.4
Comp. 393		143.0 – 146.0		268	266	266	0.26	SiO 2 (NH)	AcOEt	124.3	1.1
Comp. 394		144.0 – 145.0	325	303		301	0.27	SiO 2 (NH)	AcOEt	119.9	3.9
Comp. 395		178.0 – 178.5	303	303		301	0.29	SiO 2 (NH)	AcOEt	111.6	2.1
Comp. 396			323	301	321	299	0.29	SiO 2 (NH)	AcOEt	102.7	

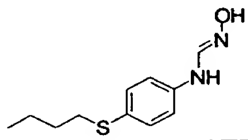
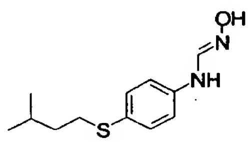
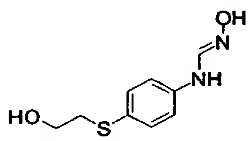
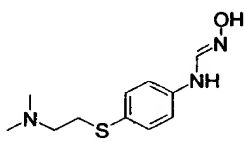
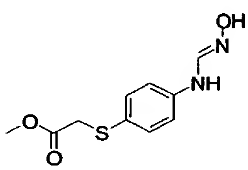
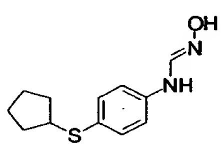
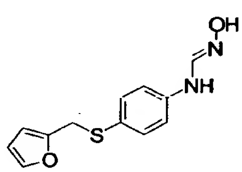
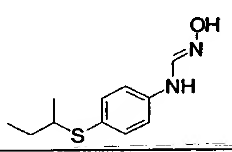
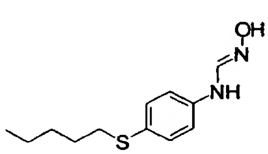
Comp. 397				319			0.29	SiO 2 (NH)	AcOEt	99.3	
Comp. 398			296	296	294	294	0.29	SiO 2 (NH)	AcOEt	95.2	2.4
Comp. 399		118–120	224	224	222	222	0.31	SiO 2 (NH)	AcOEt	102.3	98
Comp. 400		115.0 – 117.0	238	238		236	0.29	SiO 2 (NH)	AcOEt	116.9	48.7
Comp. 401		100.0 – 102.0	252	252	250	250	0.29	SiO 2 (NH)	AcOEt	117.4	37.6
Comp. 402		95.0–96.0	280	280	278	278	0.29	SiO 2 (NH)	AcOEt	118.8	18.7
Comp. 403		101.5 – 102.0	266	266	264	264	0.32	SiO 2 (NH)	AcOEt	118.3	28.5
Comp. 404		57.5–59.0	268	268	266	266	0.29	SiO 2 (NH)	AcOEt	114.9	115.6
Comp. 405			314	314	312	312	0.33	SiO 2 (NH)	AcOEt	116.0	

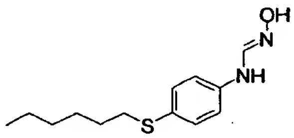
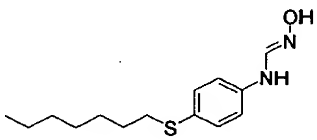
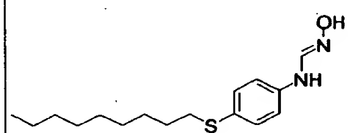
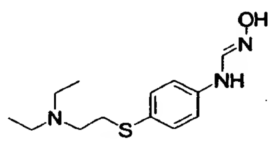
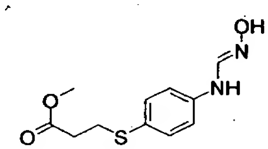
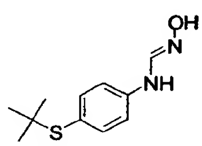
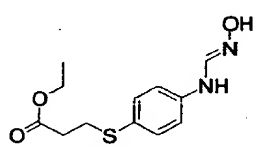
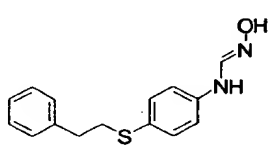
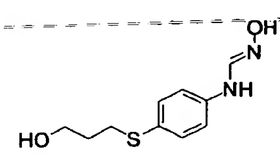
Comp. 406				359	357	357	0.29	SiO2 (NH)	AcOEt	73.7	
Comp. 407		127.5 – 129.5	264	264	262	262	0.29	SiO2 (NH)	AcOEt	94.3	4.9
Comp. 408		177.0 – 177.5	278	278	276	276	0.29	SiO2 (NH)	AcOEt	103.0	4.2
Comp. 409		145.0 – 146.0		223	221	221	0.31	SiO2 (NH)	AcOEt	113.2	6.7
Comp. 410		153.0 – 155.0		301	299	299	0.31	SiO2 (NH)	AcOEt	117.3	1.0
Comp. 411		150.5 – 151.5	246	246	244	244	0.31	SiO2 (NH)	AcOEt	122.4	3.1
Comp. 412		130.0 – 130.5	260	260	258	258	0.32	SiO2 (NH)	AcOEt	119.4	1.5
Comp. 413		112.0 – 113.0		227	225	225	0.32	SiO2 (NH)	AcOEt	120.2	2.3
Comp. 414		132.0 – 133.5	241	241	239	239	0.32	SiO2 (NH)	AcOEt	113.2	1.0

Comp. 415		114–117	264	264	262	262	0.31	SiO 2 (NH)	AcOEt	103.7	17.6
Comp. 416		99.5–102.5	264	264		262	0.31	SiO 2 (NH)	AcOEt	85.8	16.3
Comp. 417		146.5 –148	264	264		262	0.33	SiO 2 (NH)	AcOEt	102.8	90.0
Comp. 418				273	271	271	0.33	SiO 2 (NH)	AcOEt	120.4	
Comp. 419			289	289	287	287	0.33	SiO 2 (NH)	AcOEt	116.1	
Comp. 420		147–148.5	237	237	235	235	0.31	SiO 2 (NH)	AcOEt	118.6	8.0
Comp. 421		153–154.5	251	251	249	249	0.33	SiO 2 (NH)	AcOEt	113.3	3.9
Comp. 422		132.0 – 134.0	263	263	261	261	0.33	SiO 2 (NH)	AcOEt	121.6	1.5
Comp. 423		132.0 – 134.5	263	263		261	0.35	SiO 2 (NH)	AcOEt	118.4	2.2

Comp. 424		102.0 – 103.5										1.5
Comp. 425		>300										3.0
Comp. 426		101.5 – 104.0										5.1
Comp. 427		108.0 – 109.5										2.6
Comp. 428		143.5 – 144.5										51.5
Comp. 429		159.0 – 160.5										79.1
Comp. 430		139.5 – 141.0										7.4
Comp. 431		113.0 – 115.0										47.7
Comp. 432		116.5 – 117.5										19.5

Comp. 433		125.0 – 127.0									1.5
Comp. 434		>300									3.2
Comp. 435		133.0 – 134.5									2.2
Comp. 436		140.5 – 141.0									79.2
Comp. 437				293	291	291	0.33	SiO 2 (NH)	AcOEt	96.1	
Comp. 438				251	249	249	0.36	SiO 2 (NH)	AcOEt	87.9	
Comp. 439		144.1 – 144.2		211	209	209	0.36	SiO 2 (NH)	AcOEt	92.3	2.9
Comp. 440				255		253	0.33	SiO 2 (NH)	AcOEt	102.8	
Comp. 441		166		259	257	257	0.33	SiO 2 (NH)	AcOEt	94.2	

Comp. 442				225	223	223	0.36	SiO_2 (NH)	AcOEt	95.7	
Comp. 443				239	237	237	0.38	SiO_2 (NH)	AcOEt	103.0	
Comp. 444		121.0		213	211	211	0.10	SiO_2 (NH)	AcOEt	100.7	12.1
Comp. 445		112.0		240	238	238	0.18	SiO_2 (NH)	AcOEt	95.1	
Comp. 446				241		239	0.31	SiO_2 (NH)	AcOEt	95.9	
Comp. 447				237	235	235	0.36	SiO_2 (NH)	AcOEt	95.9	
Comp. 448		125.0 – 126.5		249	247	247	0.36	SiO_2 (NH)	AcOEt	109.8	1.9
Comp. 449		119.0 – 120.5		225	223	223	0.38	SiO_2 (NH)	AcOEt	105.1	1.8
Comp. 450				239	237	237	0.41	SiO_2 (NH)	AcOEt	105.9	

Comp. 451				253	251	251	0.41	SiO 2 (NH)	AcOEt	97.6	
Comp. 452				267	265	265	0.41	SiO 2 (NH)	AcOEt	112.3	
Comp. 453				295	293	293	0.44	SiO 2 (NH)	AcOEt	95.3	
Comp. 454				268	266	266	0.26	SiO 2 (NH)	AcOEt	105.8	
Comp. 455				255		253	0.28	SiO 2 (NH)	AcOEt	105.6	
Comp. 456		143.0 – 145.0		225	223	223	0.33	SiO 2 (NH)	AcOEt	94.4	6.3
Comp. 457				269	267	267	0.33	SiO 2 (NH)	AcOEt	112.6	
Comp. 458				273	271	271	0.36	SiO 2 (NH)	AcOEt	116.0	
Comp. 459		108– 108.5		227	225	225	0.10	SiO 2 (NH)	AcOEt	119.0	2.4

* SiO2(NH): Merck pre-coated plates Silica gel 60 F254, SiO2(NH)(NH): TLCplateNH Fuji Silysia Chemical LTD.

Experimental Example [Inhibitory effect of 20-HETE synthase originated from rat kidney microsome]

Regarding the compounds listed in Table 1, their inhibitory activity to production of 20-HETE was examined. This examination was carried out based on the method described in J. Pharmacol. Exp. Ther., Vol. 268, pp. 474 (1994).

The subject compound for this examination was added to a buffer comprising 50mM of 3-morpholinopropanesulfonic acid (pH7.4), 5mM of magnesium chloride and 1mM of ethylenediaminetetraacetic acid (EDTA) disodium salt.

After that, the rat kidney microsome (microsome fraction prepared from the kidney of a spontaneous hypertension rat (male, 6 weeks of age)) as an enzyme, [5,6,8,9,11,12,14,15] tritium-arachidonic acid (supplied by Amasham) as a substrate, and NADPH (supplied by Sigma) as a coenzyme were added and reacted for 1.5 hours at 37 ℃.

After the reaction, formic acid was added to stop the reaction, and then acetonitrile (final concentration of 50%) was added and left for 1.5 hours at room temperature.

The activity of 20-HETE synthase was measured by using a high performance liquid chromatograph having a detector for radioactive substances (supplied by Gilson), and equipped with a C18 reversed phase column (Biocyl C18, supplied by Bio-rad).

Setting an amount of 20-HETE production to 100% when no subject compound for examination was added, the concentration of the subject compound at which the production of the 20-HETE was inhibited to 50% and the inhibition rate at which 1 μM of the subject compound was added are presented together in Table 1.

Referring to Table 1, it was confirmed that the compounds of the present invention have inhibitory activity for production of 20-HETE.

Industrial applicability

The compounds represented by the general formula (1) or the

pharmaceutically-acceptable salts thereof according to the present invention are useful as inhibitors for production of 20-HETE. Therefore, they are useful as medicines, and in particular, therapeutic agents for various diseases in human subjects and animals, which 20-HETE is implicated in, such as kidney diseases, cerebrovascular diseases, or circulatory diseases.

In addition, in the compounds represented by the general formula (1) or the pharmaceutically-acceptable salts thereof, the compounds wherein a non-hydrogen substituent is present at the para position of the hydroxyformamidino moiety on the benzene ring are, in particular, preferable.

In addition, the compounds represented by the general formula (1) or the pharmaceutically-acceptable salts thereof as recited in Claims 5 or more are novel compounds and useful in themselves, and also, exhibit the excellent effects described above.